BIOTECHNOLOGY IN A GLOBAL ECONOMY

Volume II: Contractor Documents

Part II

1. "Biotechnology Developments in Asia -- A Financial Perspective," Michael K. Hsu, Robert T. Yuan, Daniel L. Hamilton

2. "Commercial Biotechnology in Japan," Dr. Aki Yoshikawa

3. "Environmental Biotechnology: Commercial Prospects," Sue Markland Day

4. "International Biotechnology Patenting," Harold C. Wegner

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June 1991

J952-84

BIOTECHNOLOGY DEVELOPMENTS IN ASIA
- A FINANCIAL PERSPECTIVE

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FINAL REPORT
SEPTEMBER 15, 1989

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INTRODUCTION

This study will cover the development of biotechnology in the newly industrializing countries (NICs) of Singapore, South Korea and Taiwan, and the rapidly developing nation of Thailand. Their importance to the United States is not only as potential markets for United States biotechnology products, but also as manufacturing bases and stepping stones into other Asian markets such as China, Japan and Indonesia.

All of these countries have identified biotechnology as a key technology for industrial development and is reflected in the number of government agencies in each country involved with biotechnology (Table 1). The environment for biotechnology development in each of these countries will be examined and will include: government policies (funding of R&D, tax incentives, patents and regulatory procedures); areas of research (with emphasis on the principal research institutes and their activities); descriptions of biotechnology-related industries; and, the principal mechanisms for financing biotechnology ventures.

All of the NICs have dynamic economies with annual growth rates of 8-9% and Thailand is viewed as the next likely lesser

Table 1: GOVERNMENT AGENCIES INVOLVED IN BIOTECHNOLOGY

Area	Singapore	Thailand	Korea	Taiwan
R&D	*Economic Development Board *Science Council *Min. of Education	*Science & Technology Development Board (MOSTE) *National Center for Genetic Engineering & Biotechnology	*Min. of Science & Technology *Min. of Education	*National Science Council *Academia Sinica
Industrial Development	*Biotechnology Program (EDB) *Science Council	*Science & Technology Development Board (MOSTE) *Program for Appropriate Technology in Health	*Min. of Science & Technology *Korea Genetic Engineering Research Association[1] *Korea Drug Research Association[1]	*Development Center for Biotechnology *National Science Council *Min. of Health *Min. of Economic Affairs *Min. of Defense *Min. of Communications
Agriculture	*Primary Production Department (MND)	*National Center for Genetic Engineering & Biotechnology	*Office of Rural Development (MAF)	*Council of Agriculture
Finance	*Economic Development Board	*Board of Investment	*Min. of Finance *Min. of Trade and Industry	*Min. of Economic Affairs

1. Government-industry association

Abbreviations: MOSTE - Ministry of Science, Technology and Energy
EDB - Economic Development Board
MND - Ministry of National Development
MAF - Ministry of Agriculture and Fisheries

Source: Hsu, Yuan, and Hamilton. Sept. 1989.

developed country (LDC) to join the ranks of the NICs. All four countries depend heavily on exports to the United States with the result that the United States has negative trade balances with all of them. The negative trade balances in 1987 ranged from $16 billion with Taiwan to $1.3 billion with Thailand (Table 2). The largest of the four countries in terms of area and population is Thailand which also has the lowest per capita gross national product (GNP) (less than $1,000). The smallest is Singapore, a city state of only 239 square miles. With a per capita income of $7,872, Singapore ranks second in Asia behind Japan. Taiwan has the fastest growing per capita GNP of the four, currently exceeding $5,000. The Republic of Korea (South Korea) has the largest GNP of the four, approaching $130 billion, and the second largest trade balance with the United States of this group ($9.6 billion).

Government policy in the three NICs reflects a move away from traditional manufacturing and into high technology industries with biotechnology being perceived as likely to have a major impact on a broad spectrum of industries. Thailand is interested in the application of biotechnology to its important agricultural and food processing industries.

TABLE 2.

KEY INDICATORS - 1987

COUNTRY	AREA (SQUARE MILES)	POPULATION (M)	GNP (US $B)	PERCAPITA GNP (US $)	EXPORTS (US $B) US SHARE	IMPORTS (US $B) US SHARE	US TRADE BALANCE (US $B)
SINGAPORE	239	2.6	20.5	7,872	28.6 24%	32.5 15%	-2.2
SOUTH KOREA	41,176	42.1	128.4	3,098	47.3 39%	41.0 21%	-9.6
TAIWAN	13,814	19.7	99.3	5,075	53.5 44%	35.0 23%	-16.0
THAILAND	198,114	54	47.1	879	11.7 19%	13.0 12%	-1.3

Sources: FET. Singapore. June, 1988.
FET 89-67. South Korea. June, 1989.
FET 89-36. Taiwan. Mar, 1989.
FET 89-48. Thailand. May, 1989. & Background Notes (USDOS) BPA Mar. 1988.

SINGAPORE

Government

The small city state of Singapore has undergone massive economic growth based on the shipping and petrochemical industries and on its role as a manufacturing base for foreign multinationals. However, increasing labor costs and competition from the LDCs have led the government to develop a new strategy that focuses on high technology and service industries. The government of Singapore has selected biotechnology as one of its priority areas for high technology development. Towards this purpose, it has recently set up a National Program in Biotechnology. The promotion of biotechnology has several components: an expansion of R&D and training activities, the creation of an infrastructure for high technology companies, and the aggressive use of tax incentives, tax deductions and grants to attract biotechnology companies.

The single most important government agency in both the funding and coordination of biotechnology efforts is the Singapore Economic Development Board (EDB) which is under the Ministry of Trade and Industry. A National Biotechnology Commission has been

created to implement the National Biotechnology Program with a specific mandate towards rapid commercialization of new products and processes. The Commission is composed of the director of the National Biotechnology Program, the director and two senior scientists of the Institute for Molecular and Cell Biology (IMCB), and the director of the Primary Production Department (PPD).

The single largest investment in biotechnology by the Singapore government has been the creation of the IMCB at the National University of Singapore (NUS) (see next section). The cost of this new institute has been $30 million and it is intended to be a centerpiece for modern biological research in Southeast Asia. IMCB exists as a basic research institute and as a training facility for graduate students and postdoctoral fellows. Though it is expected to interphase with private industry, it has no direct responsibility for either applied research or technology transfer. It is a matter of some controversy whether IMCB should undertake such activities or whether a new institute for technology transfer should be established.

Singapore has developed over the years a comprehensive series of tax and fiscal incentives for foreign companies, with increasing emphasis on those involved in high technology activities. Furthermore, there has been a shift in the implementation of such policies to focus on those companies that

would bring a R&D component to Singapore. Those incentives that apply to biotechnology companies are summarized in Table 3. These include pioneer status which provides tax relief for a period of 5-10 years and tax concessions for new fixed investments and for income obtained from a regional headquarters located in Singapore.

Though Singapore sees the need for attracting major multinationals, both as a source of investment and jobs, its biotechnology strategy is directed towards the creation of new biotechnology companies, particularly in the areas of human health care and agriculture. EDB has its own S$100 million venture capital fund and is able to invest directly in high technology projects, though there have been no biotechnology investments to date. EDB also has the INIT program (Initiatives in New Technology) which provides direct support for the training of workers in new technologies. This program has been used to advantage by some of the new biotechnology companies. EDB is responsible for the Product Development Assistance Scheme (PDAS) which provides grants for development of new products. The PDAS grants will support up to 50% of the direct costs of development to a maximum of S$200,000.

The other government agency involved in biotechnology in Singapore is the Science Council. Evolving from an advisory organization, the Science Council is now responsible for the

TABLE 3: GOVERNMENT INCENTIVES FOR INVESTMENT

	SOUTH KOREA	SINGAPORE	TAIWAN	THAILAND
U.S. INVESTMENT (MILLION $$)	$800	$2,300	$900	$1,100
RESTRICTIONS ON FOREIGN EQUITY	>57% PERMITTED	NO RESTRICTION	100% PERMITTED	<51% PERMITTED
CORPORATE INCOME TAX	20 - 33%	0 - 33%	22 - 35%	33%
EXEMPTIONS FROM:				
·CAPITAL GAINS TAX	EXEMPT	NO TAX	EXEMPT	NO EXEMPTION
·CORPORATE INCOME TAX	EXEMPT 5YRS[1]	5-10 YRS	5 OF 9 YRS	3-8 YRS
·TAXES/TARIFFS ON IMPORTED CAPITAL GOODS	EXEMPT	EXEMPT	UP TO 100% REDUCTION	50-100% REDUCTION
·TAXES/TARIFFS ON IMPORTED RAW MATERIALS	EXEMPT	EXEMPT	EXEMPT	UP TO 90% REDUCTION
DEDUCTIONS FROM TAXABLE CORPORATE INCOME:				
·ACCELERATED DEPRECIATION	20-100%	3 YEAR WRITE-OFF	33-50% OF NORMAL TIME	NONE
·REINVESTED PROFITS	20% OF PROFITS	NO DEDUCTION	FOR CAPITAL EQUIPMENT TO IMPROVE TECHNOLOGY	NO DEDUCTION
SPECIAL INCENTIVES FOR:				
·EXPORTERS	TAX-FREE EXPORT ZONES	PROFITS EXEMPT 3-5 YRS	EXEMPTION FROM GBRT[3] TAX	YES

1. BASED ON RATIO OF STOCK OWNED BY FOREIGN INVESTORS
2. INITIATIVES IN NEW TECHNOLOGY
3. GROSS BUSINESS RECEIPTS TAX

Source: Hsu, Yuan and Hamilton. Sept. 1989.

administration of the Science Park, the administration of the Research and Development Assistance Scheme (RDAS), promoting training in new technologies, and stimulating technology transfer. The RDAS provides grants for industrial R&D which will provide up to 100% of the development costs of major R&D projects deemed to be of national importance. The subsidized project must have local participation.

The Singapore Science park is located next to the campus of the NUS. Its location is intended to maximize the interaction between companies in the park and the faculty at NUS. Tenant companies are selected on the basis of conducting significant R&D at this site. There are currently 35 companies located in the science park of which two are in biotechnology with two more expected to move into the park in the near future.

Research Institutes and Universities

NUS is the principal institution of higher education in Singapore. It carries out basic research in biology, trains undergraduate and graduate students, and interacts with industry. NUS has eight faculties and biological research is concentrated in the Departments of Biochemistry, Microbiology, Botany, Zoology, and Chemical Engineering. Biotechnology is one of the priority

areas for R&D and projects include monoclonal antibodies, Hepatitis B vaccine, diagnostics for viral diseases, genetic improvements of plants and fermentation systems. However, it has been felt for some time that the research effort was limited, and that while theoretically the scientific staff was supposed to spend approximately 50% of their time on research, a more realistic estimate would be around 20%. Also, the degree of collaboration with industry was less than hoped for. While the university is a source of technical staff, training a fair number of undergraduates, there is a marked shortage of students at the graduate level. It was in order to expand the efforts of NUS in modern biology and biotechnology that EDB established the Institute of Molecular and Cell Biology at NUS.

IMCB opened in 1988 with the purpose of carrying out leading edge research in the biological sciences and training a pool of competent manpower at the graduate and postdoctoral levels. It would also act as a scientific resource for existing Singapore companies in biotechnology and spinoff projects for commercialization. When fully staffed the Institute will have 21 research teams comprising 200 scientists with research in the areas of cell regulation, genetic diseases and plant genetic engineering. Currently, IMCB has 13 active research teams with over 100 research scientists, 40 of whom hold Ph.D.'s. Research

activity covers new drug design, protein engineering, DNA repair, cell regulation, plant cell biology, plant molecular biology, mosquitocidal toxins, tumour immunology, tumor virology, colorectal cancer, anti-oncogenes, developmental neurobiology, stress response, and molecular neural sciences. In order to establish itself as a major international institute, IMCB has a board of scientific advisors composed of well known scientists, has actively recruited staff members in the United States and Western Europe, and regularly attracts outside speakers and visitors. (Tan, Y., 1989)

A major accomplishment of IMCB was the signing of a major research agreement in March, 1989, with Glaxo, a major multinational pharmaceutical company based in the U.K. (Yuan, 1989). A S$50 million ($25 million US) Glaxo Singapore Trust Fund was set up to finance a neurobiology research program over a period of fifteen years. Glaxo will establish the Trust with 50% of the total funds with the balance to be paid in 1993-95. There are four trustees to the trust fund: two from EDB and two from Glaxo. Research will focus on the central nervous system, particularly neural differentiation and degeneration, areas which are of particular interest to Glaxo. A group of approximately 20 scientists will be recruited under the direction of Professor Louis Lim of the Institute of Neurology in London, who is also one

of the key scientific advisers to IMCB. This research agreement is a rare instance of a major multinational funding a large and long term research program at an Asian institute. The basis for choosing IMCB for this research agreement were:

1) Glaxo has a long term commitment to activities in Singapore.

2) Prof. Louis Lim is well known in the UK and to Glaxo, and his research program fits in with the long term research objectives of the company.

3) Glaxo is a good corporate citizen and has profited from its operations in Singapore. It is in the process of expanding its existing manufacturing facilities in Singapore at an estimated cost of $50 million. EDB had actively negotiated for the establishment of R&D activities in Singapore as part of the deal.

4) EDB provided incentives for expansion of the manufacturing facility.

Though the Glaxo agreement is seen as a major coup for IMCB, it does not provide an answer to the problems of applied R&D and technology transfer. It is still unclear whether such areas of responsibility should be the province of IMCB, other departments at NUS or a new institute.

In addition to NUS, Singapore has the Nanyang Polytechnic Institute and Singapore Polytechnic Institute. These institutes have restructured their Diploma courses to train technical personnel for biotechnology-related industries, and Nanyang is being reorganized to become the second major university on the island.

The PPD is the government agency involved in agrobiotechnology projects. It is comprised of Veterinary, Agriculture and Fisheries divisions. One of PPD's major projects is the establishment of 10 Agrotechnology Parks totaling 2,000 hectares to house high-tech farms at a cost of $18.5 million (Berthelsen, 1988). These Agrotechnology Parks will increase production of high value added products (e.g. tropical fruit), and hopefully attract agricultural firms to Singapore to do R&D and then provide both new products, strains and services to countries in the surrounding region. Projects include the development of animal vaccines and diagnostic kits and virus-indexing for plants. This work is being done in collaboration with Primary Industries Enterprises Pte Ltd, the commercial arm of PPD. Also, while Singapore is phasing out pig breeding because of pollution problems it is developing pig and cattle embryo transfer.

Industry and Finance

The industrial base for biotechnology in Singapore is small (Table 4). There are some seven biotechnology companies, the majority of which are either subsidiaries of multinational firms or joint ventures with foreign companies. The new start-up companies are mainly in the areas of diagnostics and agriculture.

Two major British pharmaceutical companies (Beecham and Glaxo) use Singapore as an offshore production base, but neither of them has any R&D facilities there. However, Glaxo recently announced that it was financing a joint research program with IMCB (see preceding section). In contrast to the off-shore production strategy of the large established multinationals in Singapore, the new, small start-up companies are seeking marketing niches in Singapore that can be expanded into the surrounding region of Southeast Asia.

Diagnostic Biotechnology Private Limited was established in 1985 with an initial investment of $3 Million and with technology in immunochemistry, tissue culture, and immunoassays provided by Biotech Research Labs (U.S.). The technology transfer agreement with Biotech Research Labs is for a maximum period of seven years. 46% of the company shareholders are U.S. nationality. Starting

Table 4: REPRESENTATIVE COMPANIES WITH INTEREST IN BIOTECHNOLOGY

Category	Singapore	Thailand	Korea	Taiwan
Pharmaceuticals	Glaxo	Thai Meiji Pharmaceutical Co. Hoechst Pharmaceutical Industries	Korea Green Cross Dong-A Pharm Yunan Corp. Chong Kun Dang Corp.	Lifeguard Pharm Kuo Kuang Plasma
Diagnostics-Health Care	Scitech Medical Products Pte Ltd Diagnostic Biotechnology Pte Ltd Singapore Biotech Pte Ltd Life Technologies Pte Ltd LecTec Technology Pte Ltd		Dong-A Pharm Korea Green Cross Cheil Sugar and Co.	General Biologicals Evernew Biotech
Agriculture	Primary Industries Enterprises Everbloom Mushroom Pte Ltd Plantek Intenational Pte Ltd Multico Orchids Pte Ltd	Bangkok Flower Center Co. Thai Wah Company, Ltd	Lucky, Ltd	Taiwan Cyanamid Knowyou Seed Company
Specialty Chemicals & Food	Food Biotechnology Indus. Pte Ltd Malaysia Dairies Pte Ltd	Ajinimoto (Thai.) Co. Ltd Thai Churos Ltd Thai Theparos Thai Fermentation Industry	Lucky, Ltd Pacific Chem. Indus. Cheil Sugar and Co.	SanFu Chemicals Ve Wong Corporation Ve Dan Corporation McKay Corporation

Source: Hsu, Yuan and Hamilton. Sept. 1989.

with a staff of 15, the company now has expanded to 54 employees of which 40 are technical. *The company was granted pioneer status* for six years effective 1 February, 1985 which in effect removes its liability for corporate tax. While it lost money during the first two years ($750,000 in 1986), the company is now making a profit with projections for a profit of over $1.6 million in 1989 (profits in 1988 were approximately $1.1 million). The products on the market include ELISA-HIV-I, HIV-2 and HTLV-1 and Western Blot HIV-I, HIV-II and HTLV-I kits. 90% of the sales are exported with Taiwan being the best client. Recent profits were a result of the demand for AIDS testing of blood supplies. While most of the company's markets are in Asia, it has signed agreements with Dupont to sell test kits in Europe and has also agreed to make kits for Biorad (U.S.) to sell there too. The company is developing a more rapid AIDS diagnostic kit and hopes to develop a probe that will detect the AIDS virus before the appearance of antibodies in the blood. An ELISA assay for Dengue fever is currently in clinical trials and they are working with the Military Academy of Sciences of the People's Republic of China on a joint venture to develop hepatitis B tests. (Lim, 1989)

Another company utilizing biotechnology in the biomedical field is Singapore Biotech Pte, Ltd. Incorporated in 1983, it was adopted in principle as an ASEAN joint industrial project in 1984.

Singapore Biotech is the first ASEAN Industrial Project undertaken by Singapore with each ASEAN partner holding a 1% equity stake in the project. The company was started with a paid-up capital of $2.75 Million. The principal shareholders are Temasek Holdings Pte. Ltd., the US Summit Corporation, DBS Bank Ltd. and Intraco Ltd. Singapore Biotech has a marketing agreement with Merck for hepatitis B vaccine, at a treatment cost of about $45. Several years ago, Singapore Biotech had planned to build a manufacturing plant for hepatitis B vaccine at a cost of $20 million. That project never materialized, fortunately for the company, since the hepatitis B business seems fated to become a low profit margin one, and it now seems unlikely that the cost of the manufacturing plant would have been recovered. Singapore Biotech is in the process of expanding into a 12,000 sq. ft. facility in the Singapore Science Park. It also has marketing operations in Hong Kong, Malaysia, Australia, and Thailand. (Khong, 1989).

In addition to the agreement with Merck to market hepatitis B vaccine, Singapore Biotech is concentrating on developing diagnostics for the Asian market. Their first products are kits for nasopharyngeal carcinoma and thalassemia with markets in Singapore, Hong Kong and Malaysia. They are also interested in instrumentation with an agreement with Siemens for CAT scanners and sonic probes at the expensive end of the scale and equipment

such as ELISA scanners and electrodes at the low end. Singapore Biotech acts as sole distributor for a number of foreign companies including Boots-Celltech Ltd (UK), Connaught Laboratories (Canada), Anglian Biotechnology (UK), Amtex (USA), Diagnostic Technology (USA), Cambridge Life Sciences (UK), Australian Monoclonal Development (Australia), and Noctech Ltd (Ireland).

The other significant company in the health related field is the Scitech Medical Group. The company consists of four divisions; pharmaceuticals, diagnostics, medical equipment, and disposables. The principal market for disposables is the United States. Although, Scitech Medical is based in Singapore, it has a subsidiary in the United States servicing 2,000 hospitals throughout the country with warehousing facilities in California, Kansas, Minnesota, New York and Ontario. The principal company, Scitech Medical Products Pte. Ltd. was incorporated in Singapore in 1987. In 1988, Scitech Genetics Pte. Ltd. was incorporated. A member of the Scitech group, the latter company is to be located in the Science Park and will be involved in the manufacturing of diagnostic products and R&D in nuclear antigens, monoclonal antibodies, and related research. The Scitech Medical Products reported sales of $6 million for 1988. Among agreements of note is a licensing agreement with the NUS to develop and manufacture diagnostic products in Singapore for international marketing. In

addition to the United States, Scitech markets include Japan, Korea, Taiwan, Hong Kong, Australia and the ASEAN countries. The principal funding has come from Plexchem, Goldmark, and Mashaal Enterprises. In addition to disposables and diagnostics, the group plans to manufacture hepatitis B vaccine and develop hepatitis A and B and Dengue fever diagnostics. While the company is currently small (18 staff) it is likely to increase in size with the move into the Science Park. The major source of technology is from Israel or companies with Israeli ties such as General Biologicals (U.S.). (Mashaal, 1989)

In the area of agricultural biotechnology, two firms lead the way in Singapore, Everbloom Biotechnology Ltd. and Plantek International. Everbloom was established at the end of 1979 by a NUS researcher, Dr. Tan Kok Kheng, who had developed a process of growing shiitake mushrooms using saw dust and a defined nutrient media. Everbloom Biotechnology Ltd. was established with a loan ($551,000) from the EDB's Small Industries Finance Scheme. In 1984, Intraco, Ltd. and Frazer and Neave invested an additional $459,000 each. Their shares were purchased back in 1986. Recently, Everbloom has received additional capitalization from Prima Mills. The shiitake mushroom has a world wide market valued at over $1 billion. (Asiaweek, 1988). Everbloom's technology allows for the cultivation of the mushroom in months rather than

years. Everbloom has six licensing agreements for the use of its technology in New Zealand, Indonesia, Sri Lanka, Australia and Scotland. The Scotland agreement is a joint venture with the button mushroom producer Dumbreck with Everbloom owning 47% of the joint venture. Everbloom is interested in developing business in the United States, particularly in the East Coast. At present, no real R&D is being conducted, but there is interest in developing R&D aimed at the anticancer and cholesterol lowering properties of the shiitake mushroom. (Tan, K., 1989)

Plantek International was started in 1983 as a joint venture between Native Plants Inc. (NPI) of Utah and the Tata Group of India. The original partners were later joined by Sumitomo and Kyowa Hakko from Japan, and Intraco from Singapore. NPI retained 37% of the joint venture and Tata 27%. The technology to start Plantek was provided by NPI with the initial strategy to carry out micropropagation of tropical crop plants. Plantek provides two types of services: research production and contract production. Tropical crop plants have not turned out to be a particularly profitable business sector, so Plantek has moved into other project areas such as ornamentals and tropical fruits. In the fall of 1988, they signed an agreement with U.S. Agency for International Development (USAID) to research commercial scale tissue culture propagation of trees (Eucalyptus, Acacia, and

Leucaena species). The technique of tissue propagation is expected to increase the supply of high quality plantlets for the farmers of Southeast Asia. Another potential business area is that of gene mapping. Gene mapping identifies the locations of important genes and may be used to accelerate plant breeding programs. (Asian Agribusiness, 1988).

Two years ago, Plantek expanded but since then has run into significant difficulties, particularly in financing its activities, which forced them to cut back their staff. Currently the staff is comprised of 58 people, including three in marketing, five in R&D and 40-50 in operations. The activities of Plantek are linked in large part to those of NPI which has had its own financial difficulties. In spite of this, NPI has provided additional funds for the Plantek operations, and appears committed to it.

Another company which warrants mention though it is not by strict definition a biotechnology company is Life Technologies Pte. Ltd. This is a biomedical instrumentation company which has developed an integrated robotic system which can be used to run diagnostic tests. These systems have a potential market in the area of infectious disease diagnosis, such as AIDS, since the robotics can minimize human contact. This project was supported by the PDAS.

Companies interested in establishing themselves in Singapore have a variety of venture capital funds to draw upon for support. Funds are available from EDB's Venture Capital Fund and several privately managed funds. Besides providing seed capital, these funds can also be used to co-invest with potential investors in new technologies, including biotechnology. The other venture capital funds include Transtech Capital Investments, Intervest Ventures and DB Ventures. A number of trading companies (i.e., Temasek Holding, Intraco, Pac-Ven, and South East Asia Ventures Investment [$70 million], and Advent), are also looking for biotech opportunities, generally in the $1 - 3 million range (while not large by U.S. standards, there is often the opportunity to enter immediately into second phase funding). To date, only one investment has been into biotechnology, that being Singapore Biotech. The major problem with venture capital investment in Singapore is the lack of sufficient resources to evaluate the investments. Currently, for most of the evaluations, the venture capital funds use IMCB or NUS. While there is more money available in Taiwan, Singapore remains attractive because of a very good business infrastructure. (The Asian Venture Capital Journal, 1989)

Summary

In terms of per capita GNP, Singapore is the second richest country in Asia. Its early success in economic development and its present strategy to become a major financial and high technology center has been based on certain clear cut advantages:

1. Effective government policy in several areas: development of a scientific infrastructure, a well thought out program of tax and fiscal incentives, and support for new small companies.
2. Good training programs for technical staff.
3. A favorable business environment.
4. Honesty in government.
5. The existence of an international, multiracial, English speaking society.
6. One of the best airports in the world with excellent air links to major cities and an excellent telecommunications system.

In developing biotechnology, Singapore also has some disadvantages, the most major of which is the smallness of its population base which makes it unlikely for it to develop a major R&D infrastructure. To meet its requirements for senior

scientists, and technical and financial managers, it will have to actively recruit overseas. Its biotechnology industrial base is made up of small new companies, and their ultimate success depends on their gaining access to the regional markets of Southeast Asia, and perhaps in the long term, the markets of China and Japan or the United States and Western Europe. The financial community in Singapore is fairly conservative, and the degree of investment in biotechnology has been fairly limited.

However, taken in balance, Singapore is a good location in which to carry out the initial phases of a business operation in Asia. Business practices are straightforward, and in the case of appropriate projects, it will receive active encouragement from the government. The living environment is international in character and, therefore, much more acceptable to expatriates. Its geographical location provides easy access to the markets of Southeast Asia and its long history as a trading center provides it with a wealth of marketing networks.

THAILAND

Government

Thailand is a developing country and many aspects of government policy are related towards the establishment of a basic economic infrastructure, particularly in the agricultural sector. However, the Thai government recognizes that national development will require the introduction of certain new technologies. Biotechnology has been selected as one these key technologies, but unlike some of its neighbors, Thailand does not have a national program in biotechnology. The ministry responsible for scientific development is the Ministry of Science, Technology and Energy (MOSTE) two components of which are involved in biotechnology development; the Science and Technology Development Board (STDB), and the National Center for Genetic Engineering and Biotechnology.

The stated mission of STDB is: "The Science and Technology for Development Project is a long-term effort being undertaken by the Ministry of Science and Technology, with USAID assistance, which is aimed at helping Thailand to increase its capability to identify, develop and produce the scientific knowledge and the technology it requires to resolve problems which hinder its

industrial and agricultural development." USAID is investing $37 million over 7 years (starting in 1986) in this project. STDB provides financial support to both universities and companies. In the case of universities, this support is in the form of grants. In the case of companies, it is provided as loans for R&D with the company putting up 50% of the costs, 25% is from the Thai government and 25% is from USAID. The interest rate is 10%, and STDB retains 25% of intellectual property rights. If the funded project is commercially successful, the company will pay royalties to STDB; if it fails, the company will only be liable for the loan and the interest. It is estimated that approximately $1.5 million of the STDB funds are being used to support biotechnology projects. The Science and Technology Development Project is the only case of U.S. government funding of biotechnology R&D in the four countries under study. STDB is one of the most influential factors in the development of Thai biotechnology even though there is open criticism about the amount of bureaucracy involved in its administration (e.g. grants require review by six separate government agencies including USAID). (STDP, 1988)

The National Center for Genetic Engineering and Biotechnology (NCGEB) was established in 1983 and has a budget of approximately $1.5 million/yr which is used to fund about 50 projects at a level of $20,000-30,000/project. It supports work in both basic

research involving rDNA technology and in biochemical engineering and downstream processing. This work can be done either in universities or in industry with a particular emphasis on university-industry interactions. Priority has been given to:

- industrial applications,
- agricultural applications,
- public health, energy and environmental applications,
- strengthening of scientific infrastructure in biotechnology.

The Center has been handicapped by its limited budget which is not sufficient to meet its ambitious goals. There is some hope that the new government with its interest in developing R&D may increase the budget. It is difficult to determine the annual government budget for biotechnology, but estimates range from $7-14 million. (STDP, 1988)

The Program for Appropriate Technology in Health (PATH) is a non-profit government organization funded by the World Health Organization (WHO) and USAID. Its objective is to focus on new technologies for primary health care. PATH provides loans for projects that will promote development of new scientific findings for production in Thailand, and make the new products available to the general population. PATH has setup the International Loan Fund for Health Technology which makes available funds for

establishing production facilities for critically needed biomedical products.

The Board of Investment is the government agency that approves investments and administers the various tax and fiscal incentives (see Table 3). The Board plays the dominant role in promoting the formation of new companies.

The area of intellectual property rights is a major concern for the United States and Thailand. There is no patent protection on pharmaceuticals, and Thailand is considered to be one of the worst offenders in the copying of a broad variety of products. The U.S. government has put a great deal of pressure on the Thai government to comply with section 301 of the U.S. Trade Law which deals with intellectual property protection as it applies to computer software, pharmaceutical patents, and trademarks. If Thailand does not comply, the United States can take action by the removal of Generalized System of Preferences privileges. Thailand has been mentioned on a priority list of eight countries to be watched for progress towards resolving these issues.

Research Institutes and Universities

Research in the biological sciences is mainly carried out in the universities. The principal universities with biotechnology related research are: Mahidol University, Chulalongkorn University, and Kasetsart University, all located in Bangkok. Mahidol University is considered to have the strongest program in the biological sciences with a strong emphasis on the biomedical area. It has a Center for Biotechnology, and a Center for Molecular Genetics and Genetic Engineering. Mahidol University also has the National Vaccine Center which was inaugurated in early 1987. It is the first one of its kind in Southeast Asia and was built and equipped at a cost in excess of $5 million with the Italian government contributing $3 million worth of equipment. The University has under development vaccines against dengue hemorrhagic fever, malaria, and hepatitis B. The Vaccine Center is negotiating with some major manufacturers of vaccines for production contracts at its own facilities outside of Bangkok. (Bhamarapravati, 1989)

Chulalongkorn University has developed research in molecular biology and has an Institute of Biotechnology and Genetic Engineering. It is known for aquaculture of shrimps, rice tissue culture and processing technology.

Kasetsart University specializes in various areas of agricultural technology including tissue culture for improvement of propagation of various plants, embryo transfer technology and fermentation technology. It has a Plant Genetic Engineering Unit/Central Laboratory and Greenhouse.

The science base in biotechnology in Thailand is basically that of a developing country. In the biomedical area, its principal strengths are in vaccines and tropical infectious diseases. Thailand's major research capabilities are associated with agriculture and food processing, including plant tissue culture and plant breeding, fermentation technology, and industrial enzymes. Diffusion of biotechnology into the various research establishments has been slow but is expected to speed up under the present government which has placed a stronger emphasis on R&D both in the public and private sectors. Another severe limitation is a shortage of researchers experienced in modern molecular and cell biology as well as their applications to agriculture and human health care.

Industry and Finance

There are no biotechnology companies in Thailand nor established companies with significant biotechnology activities.

Given the importance of agriculture to the Thai economy, there is growing interest in the introduction of agricultural biotechnology in order to increase crop yields.

The principal Thai companies that can apply biotechnology to their present business activities are listed in Table 4. Many of these companies perceive themselves as having to diversify, particularly by moving into high technology industries with different requirements for both physical plant and personnel. If and when they move into new business areas, their main thrust will take place in the application of biotechnology to food processing and agriculture (including ornamentals) and production of vaccines such as a vaccine against foot and mouth disease being developed as a government sponsored project.

The banks are important institutions for financing the introduction of new technologies into agriculture. Two of the principal banks involved are: Bangkok Bank and Thai Farmers' Bank. They provide funding through loans and direct equity investments particularly in technology projects in agriculture and food processing. The Bangkok Bank is the largest bank in Southeast Asia with branches in virtually every Asian country. It is willing to fund foreign joint ventures and foreign companies which are willing to set up operations in Thailand. The Thai Farmers Bank is one of the most progressive and is active in the human

health care area and has been a participant in the PATH program.

The Bank of Agriculture and Agriculture Cooperatives is Thailand's foremost credit institution which is responsible for promoting the government's agricultural development plans. It promotes those aspects of agriculture that would increase Thai food exports particularly in the area of fruits and vegetables. The Bank tries to bring together public and private sector institutions into contact with farmers. It provides credit to those farmers and farmer organizations that can then make the necessary investments. (Bank for Agriculture and Agricultural Cooperatives, 1988).

The Asian Development Bank (ADB) is the largest bank in Asia with the majority of the funds coming from the U.S. and Japanese governments. Its purpose is to develop an infrastructure to improve the technology of existing industries and to develop new industries. Since 1983, the ADB has placed an increasing emphasis in its efforts to directly promote healthy private sectors in its DMCs and it has recently identified venture capital as a potentially important tool in that process. ADB is now one of the key players in investing into Asian venture capital funds. ADB believes that the establishment of a strong venture capital industry can contribute significantly toward private risk capital mobilization for investment into new technologies including

innovative biotechnology. This would be of particular importance to companies initiated by entrepreneurs with sound business plans but limited capital resources. Its principal thrust in Thailand is to increase the capabilities of the Thai agricultural industry mainly through the funding of venture capital companies. Such venture capital companies would then assist in the creation of new private companies involved in agricultural biotechnology. (Tusaka, 1988)

The strong economies of Taiwan, S. Korea and Singapore preclude a major role for ADB in those countries. However, in Thailand, ADB is a very visible institution which has currently invested in the Thailand Agribusiness Venture Company (TAVC), managed by Venture Capital Company Ltd (VCC), a subsidiary of Thai Financial Syndicate - a major financial institution.

Venture capital in Thailand is at an early stage of its development, but a number of international organizations have been working with Thai banks. The Business Venture Promotion (BVP) fund ($6 million) involves a collaboration between USAID and six Thai banks while the Thai Agribusiness Venture Co. ($10 million) is funded by ADB and the development agencies of two European countries. The Thai Financial Syndicate, composed of twelve Thai banks, will fund agricultural biotechnology projects (open ended funding) through its subsidiary VCC. VCC will consider two

different types of proposals: high tech projects with a partner that has an appropriate technology from the United States or one of the NICs, or an agricultural project with Thais providing the land and the foreign partner providing capital and technology. Semaco ($4.5 million) has support from Commonwealth Development Corporation (UK) and Rockefeller Bros (US). SEAVI (Southeast Asian Venture Investments, Ltd) is a Singapore fund with an operation in Thailand. There is also an offshore fund called Thai Venture Capital Corporation ($30 million) based in the Netherlands. There are no funded biotechnology projects to date and there is relatively little interest in projects in human health care or pharmaceuticals, but there is considerable interest in agriculture, food processing, and to a lesser extent biomedical devices and instrumentation. (The Asian Venture Capital Journal, 1988)

Summary

There is considerable interest on the part of the Thai government and associated international and foreign development programs in biotechnology. However, there is no focused government policy towards biotechnology and its applications. MOSTE is the ministry charged with scientific development, but it

is a relatively junior organization lacking both sufficient resources and political influence. The efforts on the part of STDB and the National Center for Biotechnology and Genetic Engineering are limited and directed primarily towards support of research. Increased efforts in biotechnology would require increased funding and better coordination. On the industrial side, government incentives, particularly for U.S. companies, are competitive with those of the NICs (Table 3). Patent protection is a major problem which hopefully will be resolved through negotiations with the United States during the next two years. At the present time, this is a distinct disincentive to major investments in biotechnology. It should be noted that there should be an improvement in the high technology industrial sector due to the attitudes of the new government.

The scientific base for biotechnology in Thailand is relatively small. There has been a major effort to establish biotechnology centers at three of the national universities including the National Vaccine Center. There is little evidence of coordination of the research efforts between the various institutions. The best biological research in Thailand is in the area of agriculture and vaccine development. It seems that Thailand has two major options: an expansion of its current research establishment which would be expensive both in terms of

funds and of manpower or a continuance of the present low level of research funding and acquisition of the appropriate technologies from abroad. It is useful to point out that the other countries in this study have chosen to commit significant funding to the build-up of their research establishments.

A biotechnology industry in Thailand is yet to be born. It does not exist either in the form of small new biotechnology companies or in that of novel products in established corporations. The potential, particularly in the agrobiotechnology sector, is considerable as is interest on the part of both established companies and financial organizations. Furthermore, a number of foreign development institutions are also interested in the introduction of this new technology into Thai agriculture. Given the limited size of the Thai biotechnology establishment, any commercial project would require the participation of foreign companies or institutions. Foreign agricultural companies look at Thailand as a country with good economic prospects and therefore as a good location for joint ventures. For Asian companies it also provides the additional attraction of using Thailand as a base for developing business in the Indochina peninsula.

The situation in Thailand is that of a country undergoing a transition from being an LDC to becoming the next NIC. The system

is changing extremely rapidly, but the negotiation of agreements with Thai companies is a time consuming and laborious exercise. Their successful conclusion very frequently involves the use of consultants and intermediaries that represent a not insignificant business cost.

REPUBLIC OF KOREA (SOUTH KOREA)

Government

The economy of South Korea is dominated by 'chaebols', major industrial conglomerates, whose growth has been tightly linked to technology transfer from the United States and Japan. In 1987, Korean firms signed 637 technical licensing agreements with foreign companies, 28% of them with U.S. firms. In the first half of 1988, 359 agreements were signed, 99 with U.S. firms. These agreements brought $95 million to U.S. companies alone in the first half of 1988. The number of agreements with Japanese companies did not lag far behind the United States. (FET 89-67)

Desiring a better industrial balance between the chaebols and smaller companies, and a more advanced indigenous research base, the Korean government has given high priority to certain technologies for industrial development. Biotechnology is

considered a key technology because of its applications in the pharmaceutical, food processing, and specialty chemical industries. Korean government policy has two principal objectives: the expansion of the scientific infrastructure and the promotion of research in private companies. In 1984, the government passed the law for the Promotion of Genetic Engineering, thus providing the legal basis for biotechnology programs in various government ministries, funding for R&D, and establishment of a Genetic Engineering Research Institute.

The major government ministry involved in biotechnology is the Ministry of Science and Technology (MOST). In addition, the Ministry of Agriculture and Fisheries, and the Ministry of Education are active participants in biotechnology development, the former with plant and animal breeding, and the latter in university research and training.

MOST has selected several principal technologies as being important to the industrial development of biotechnology in Korea and these include: recombinant DNA methods, hybridoma techniques, large scale tissue culture, bioreactor design, gene transfer in plants, and microbial techniques. Financial support for individual projects is dependent on whether it fits into the goals of the defined National Projects which are:

- Bioresources (embryo transfer and artificial seeds)

- Bioprocessing (industrial use of enzymes and bioreactor design)
- Genetic Engineering (including monoclonal antibodies)
- Microbial Biotechnology (isolation of new strains, soil microbiology)

The majority of government biotechnology R&D funds go to the Korean Advance Institute of Science and Technology (KAIST), the Korea Research Council for Applied Genetics (KORCAG) or the Korea Genetic Engineering Research Association (KOGERA). The Genetic Engineering Research Center at KAIST awards grants to individual laboratories with KORCAG acting as the peer review body. KOGERA is a collaborative effort between industry and MOST with the government providing up to 70% of the research funds. Its mission includes promoting the industrialization of genetic engineering and biotechnology, administering the research foundation, initiating policy improvements, coordinating collaborative R&D projects, training and educating experts, collecting and supplying information on technology, organizing meetings and addressing relevant industrial issues. KOGERA has 19 industrial members who produce biotechnology related products ranging from pesticides to cosmetics (Table 5). (Han, 1989)

Another government-industry consortium is the Korea Drug Association which has 17 company members and had a budget of

TABLE 5: KOGERA MEMBER FIRMS 1989

COMPANY	MAJOR BIOTECHNOLOGICAL PRODUCTS
KOREA GREEN CROSS CORPORATION	PHARMACEUTICALS (ALBUMIN, UROKINASE, -INTERFERON, VACCINES)
DONG-A PHARMACEUTICAL CO.	PHARMACEUTICALS (DRINKS, DIGESTIVE ACIDS, ANTIBIOTICS, ENZYMES)
ORIENTAL BREWERY, LTD.	BREWERY (ALCOHOLIC BEVERAGES, BEER)
LUCKY, LTD.	CHEMICAL (GLUCOSE, SORBITOL, HFCS)
KOHAP LTD.	FOODS (CYCLODEXTRIN, AMINOACID)
SEOUL MIWON CO., LTD.	FOODS (MSG, LYSINE, GLUCOSE, HFCS)
YUNAN CORPORATION	PHARMACEUTICALS (RIFAMYCIN, STEROIDS)
CHEIL SUGAR AND CO.	FOODS (MSG, SUGAR, NUCLEIC ACID)
CHONG KUN DANG CORP.	PHARMACEUTICALS (TETRACYCLINE, RIFAMYCIN)
PACIFIC CHEMICAL INDUSTRIAL CO.	COSMETICS (ENZYMES, ANTIBIOTICS)
HANKUK YAKULT MILK PRODUCTION	FOOD (FERMENTED MILK DRINK)
DONG-SHIN PHARMACEUTICAL CO.	PHARMACEUTICALS (ANTIBIOTICS, VACCINES, ETC.)
HYUNDAI HEAVY INDUSTRIAL CO.	MACHINERY
YU KONG LIMITED	PETROCHEMICALS
IL-DONG PHARMACEUTICAL CO.	PHARMACEUTICALS (DRINKS, DIGESTIVE ACIDS, ETC.)
KOLON INDUSTRIES, INC.	PETROCHEMICALS, SYNTHETIC FIBERS, PLASTICS
KOREA STEEL CHEMICAL CO.	PESTICIDES, PETROCHEMICALS
KOREA EXPLOSIVES CO.	PESTICIDES, CHEMICALS
YOUNG JIN PHARMACEUTICAL CO.	PHARMACEUTICALS

Source: Han, 1989.

approximately $1.2 million in 1987 (30% from the government). Group projects such as the New Drugs Project can receive up to 50% of their funds from MOST. The Korea Science and Engineering Foundation (KOSEF) provides funds for fellowships and conferences. (Han, 1989)

In addition to supporting R&D the government has also established four venture capital organizations: Korea Technology Development Corporation; Korea Technology Advancement Corporation; Korea Development Investment Corporation; and, Korea Technology Finance Corporation. (see section on industry and finance).

The government of Korea has been cognizant of the concerns of foreign firms regarding the unauthorized use of copyrights, patents and trademarks and in July, 1987 passed news laws for the protection of intellectual property rights. Korea has also joined appropriate international conventions including the 1987 Budapest Treaty. Although Korea has established an interagency task force headed by the Ministry of Trade and Industry to ensure effective enforcement, foreign firms are nevertheless still concerned about the effectiveness of these new regulations.

Universities and Research Institutes

The universities in Korea, unlike those in the United States are predominantly concerned with training undergraduates. South Korea is also unique in that unlike most Asian countries, there are more private than public universities. The most noted of the universities are Seoul National University (public), and Korea University and Yunsai University (both private).

Seoul National University is considered the premier university in South Korea. The University has departments of Chemistry, Microbiology and Zoology which have produced the country's most distinguished biological scientists. While its principal responsibility is the training of undergraduates, it is attempting to increase its research activities and is expected to open a new Institute for Molecular Biology and Genetics this year. The new institute will consist of three basic and three applied research laboratories. The basic research labs will be in cell and molecular biology, molecular genetics, and biochemistry and biophysics. The three applied labs will be medical biotechnology, energy and materials, and agriculture and environmental biotechnology. Grant support comes primarily from MOST, with some funding coming from KOGERA and the Ministry of Education.

Korea University is the most important of the private universities. To an even larger degree, private institutions concentrate on teaching. Furthermore, they must compete for research funds with the public universities and institutes which are more likely to receive preferential treatment from the government. Therefore, it is very difficult for Korea University and the other private schools to expand or even maintain a substantial research capability.

Realizing that there was a severe need for a major center for biotechnology R&D, the government created in 1985 the Genetic Engineering Research Center at KAIST. This is the most important component of the science base in South Korea and has a dual role as a research center and as a funding organization for academic research. Funds to support the Center come mostly from KAIST and MOST. The Genetic Engineering Research Center is composed of 15 laboratories in the Division of R&D and four programs in the Division of Technology Services. The R&D laboratories are: molecular biology, molecular genetics, protein chemistry, cell biology, microbial technology, microbial resources, microbial ecology, applied microbiology, microbial genetics, bio-control, nutrition and physiology, food biochemistry, and food resources systems. The four programs of the technology services are: biological reagents, bio-potency evaluation, a gene bank, and a

pilot plant. As with the other Asian countries, hepatitis B vaccine production is an important project area that is a major focus of the research efforts. In addition, gene synthesis and development of vector systems, production of monoclonal antibodies, and nitrogen fixation represent other major research areas. (Yuan, 1988)

The Rural Development Administration maintains a principal biotechnology laboratory. It is located in the Agricultural Sciences Institute which is composed of two departments, Chemistry and Biology, which are further subdivided into four and five divisions, respectively. The biotechnology division is part of the Biology Department and has one of the best facilities in South Korea outside of industry. The Institute has a relatively large staff of about 250, but less than 40 are Ph.D.'s. (Yuan, 1988) Furthermore, the Institute has only weak ties with the Genetic Engineering Research center and the universities.

Basically, the Korean science base is weak and funding, while on the increase in the last couple of years, is low by U.S. standards. The government does not have a comprehensive plan for expanding the research effort or for developing effective university-industry interactions. The view is widely held that the initiative for building up biotechnology is most likely going to come from the private sector. While there is a government

commitment to increase the science base, there is also an effort by industry to gain access to U.S. technology through the establishment of research facilities in the United States.

Industry and Finance

Of the four countries covered in this report, South Korea has, by far, the largest industrial base with an active interest in biotechnology. This is reflected by the number of companies (nineteen) that have membership in KOGERA. The biotechnology related industries include the food industry with its tradition of fermentation, and the growing pharmaceutical industry. The latter is highly fragmented with over 300 companies producing a variety of patent medicines and generic drugs. Major international pharmaceutical firms have a presence in South Korea mainly in the form of joint ventures, including over a dozen with American firms. Dong-A is the largest of the Korean pharmaceuticals followed by Chong Kun Dang and Yuhan. Dong-A has approximately 10% of the market while the latter two have about 5% each. While the pharmaceutical companies have shown that they can acquire and use new technologies, they often operate at low profit margins and, as a consequence, have limited resources to fund R&D. The larger chaebols, while having the financial resources, lack the

experience of conducting R&D to develop new products. KOGERA and the Korea Drug Research Association were formed in part as an attempt by the government to help alleviate some of these problems.

Dong-A Pharmaceutical Company is the largest of the pharmaceutical companies in Korea with FY'87 (ended Mar. 1988) sales of $271 million. Dong-A was the first pharmaceutical company to establish a research laboratory (1977) and recently moved into a newly built GLP building. They spent 6 billion won to construct the building containing 6,600 sq.m. and plan to double the space by 1991 with the construction of a second identical building. (Dong-A, 1988)

Biotechnological research began in the early 1980's with the establishment of the Bioengineering Lab. This resulted in the development of a diagnostic reagent for the detection of Hepatitis B in 1985 and a diagnostic reagent for AIDS detection in 1986. Other projects include the use of monoclonal antibodies for in vivo imaging and drug targeting for cancer treatment, production of interleukin-2 and colony stimulating factor, and rDNA hepatitis vaccine production. The company has also sent their researchers to be trainees at Sloan-Kettering Institute for Cancer Research and to the University of Georgia in the United States and to the Biology & Organic Chemistry Research Institute and Otsuka

Pharmaceutical Co's Research Institute in Japan. Dong-A has entered into a number of joint ventures. Included are joint ventures with companies in Japan (Meiji Seika to produce kanamycin and Sinto Kogio for antipollution devises), and the United States (Johnson and Johnson to produce baby care products and E.R. Squibb & Sons to produce high quality therapeutic drugs). The Squibb joint venture developed after years of a successful technical assistance agreement.

The principal manufacturer of antibiotics in South Korea is the Chong Kun Dang Corporation. Its fermentation plant is the largest in South Korea and its facilities conform to Good Manufacturing Practices. Its principal products are tetracycline, oxytetracycline, rifampicin and its intermediates, and erythromycin. While it maintains a central research lab with departments of pharmaceuticals, chemical synthesis and fermentation, Chung Kun Dong obtains much of its technology through licensing agreements with foreign firms. These agreements include ones with Rhone-Poulenc (France), Hoffman-La Roche (Switzerland), Beecham (United Kingdom), and Syntex (U.S.). (Chong Kun Dang, 1986)

Korea Green Cross is the major producer of Hepatitis B vaccine purified from plasma in South Korea. It also has a major business area in blood products. They are utilizing rDNA

technology to develop TPA and hepatitis vaccine and are trying to characterize biologically active substances from oriental medicines.

Pacific Chemical Co. reported net sales of over $440 million in 1988. Most of the sales are in the consumer area, i.e. cosmetics, toiletries, foods. In 1978, Pacific Chemical established the Pacific R&D Institute to strengthen productive competiveness, to develop advanced technologies, and to increase investment returns. Products developed include hyaluronic acid and propionic acid used in cosmetics, a natural sweetener extracted from stevia leaves, and in the area of enzymes, a microorganism was developed for waste-water purification. Pacific Chemical recently completed the construction of the countries most extensive enzyme production plant at Seoul's satellite city of Ansan. Cost of the project was 10 billion won ($15 million). (Pacific Chemical, 1988).

Two chaebols have major activities in biotechnology. These are the Samsung Group and the Lucky-Goldstar conglomerate. Cheil Sugar & Co. (1987 sales of $758 million) is one of the major companies in the Samsung Group (1987 sales exceeding $20 billion) with activities in biotechnology. Having a background in fermentation technology the company adopted biotechnology when it moved into pharmaceuticals and established a genetic engineering

group in 1981. As part of their long term commitment to biotechnology, Cheil Sugar established two research centers in 1983, the Research and Development Center in Ichon-kun and Eugene Tech International. Eugene Tech is an American research institute consisting of prominent Korean scientists, with advanced research facilities located in Allendale, New Jersey. The principal products include L-phenylalanine (essential ingredient for aspartame, an artificial sweetener), hepatitis-B vaccine, immuno-diagnostic tests for pregnancy, viral hepatitis and several types of cancer, an ointment of alpha interferon for viral infections and "Beta-feron", a beta-interferon preparation for use in treating viral hepatitis B. In spite of the research facilities, many of these products were developed by technology transfer from foreign companies. (Cheil Sugar, 1988).

Lucky-Goldstar has also made major commitments to the use of biotechnology to enhance its product line. Lucky Limited, the conglomerate's chemical company) was originally a manufacturer of cosmetics, but has moved into specialty chemicals, petrochemicals and consumer products. While not a major pharmaceutical producer, it plans to use biotechnology to move into this area. All of the company's biotechnology research in South Korea is centered at its research facilities in the Taedok science town. As with Cheil Sugar, Lucky has established a company in the United States, Lucky

Biotech. Lucky Biotech currently has 20 employees housed in facilities rented from Chiron Corporation. They recently announced, however, the purchase of land in an industrial park in Hercules, California for $1.6 million in cash. Plans are to build a research facility and pilot plant there over the next three to five years and to increase employment into the hundreds. The principal objective of Lucky Biotech is to clone and express a series of growth hormones and transfer the strains and technology back to Korea for further development. (Biotechnology Newswatch, 1989).

Financing of biotechnology ventures in South Korea is dependent on the partner. In the case of a chaebol, they have sufficient funds to finance new operations from within the organization with no need to seek outside capitalization. In these cases, the new company (including some set up in the United States), are wholly owned subsidiaries. For the small and medium sized companies, through the active encouragement of the Ministry of Finance, several venture capital funds were established. Korea Development Investment Company (KDIC), established in 1982, is run as a private company with active support from the government. KDIC will provide medium and long-term capital through equity and equity-type investments. In addition to providing capital, KDIC expects to serve on the board of directors of the invested

companies. The majority of investments are expected to involve the use of new technologies either developed locally or transferred to Korea from abroad. Currently, KDIC has investments in 33 Korean companies with the amount invested in each company on the order of 100 million to 200 million won ($150-300,000). The types of companies that KDIC has invested in include electrical and electronic, chemicals and mechanical and metal engineering. While no investment in biotechnology is known to date, this area has potential for funding. The Korea Technology Finance Corporation (KTFC) was established in 1984 with a paid in capital of 20 billion won ($30 million) by the Korea Development Bank. KTFC provides financial and related services to small and medium enterprises such as supporting R&D costs, the initial commercialization of new technology, improvement of manufacturing processes, import of technology and/or adaptation and improvement of imported technologies and the procurement and utilization of foreign specialists and technology advisers. As with KDIC, no investments have been made into biotechnology to date.

SUMMARY

As in the case of the other NICs, South Korea is trying to move away from traditional manufacturing and into high technology

industries. However, unlike the others, South Korea has an extensive manufacturing sector ranging from electronics to ships. In many respects, economic development in South Korea has many similarities to Japan. The economy is dominated by a number of major industrial conglomerates which act in conjunction with the government. In the early 1980's, South Korea had a bout of the same "biotechnology fever" that had affected the United States and Japan. This fascination with the commercial implications of biotechnology affected a significant number of companies. The largest investment into biotechnology R&D has come from the chaebols, but some of the larger pharmaceutical companies have also established biotechnology research facilities. Therefore, the single most important factor in the development of biotechnology in South Korea is the involvement of the private sector in both research and development of new products. This has been stimulated by collaboration with the government in creating semi-public research associations targeted towards certain technologies. The financing of such new activities is through borrowing rather than equity. Therefore, South Korea has experience in the adaptation of new technologies and has the capital necessary for investment. What is lacking is the experience in doing basic research in the biological sciences and commercializing its results particularly when this requires

lengthy clinical trials or extensive field testing. This problem is compounded by a shortage of skilled manpower ranging from scientists versed in genetic engineering or bioprocessing to technical administrators and senior managers. One unusual approach to this problem is the establishment of new biotechnology companies in the United States which basically carry out R&D for its parent company. Such firms would have access to the most recent scientific developments taking place in the United States and also act as licensing agents.

Government policy has had two main objectives: expansion of the research base and technology transfer into the industrial sector. The mechanism of creating research associations is too recent to be able to judge its effectiveness. The government is committed to expanding both research and training in the biological sciences, but the level of funding is still low, and there is a lack of coordination in the research efforts. The number of experienced investigators capable of carrying out work at an internationally acceptable level is also a limiting factor. There are those who feel that part of the problem is that MOST is a relatively minor ministry with limited funds and insufficient political influence.

Perhaps to a greater extent than the other NICs, South Korea seem to be intent in developing technologies on their own or with

the help of Korean expatriates. This limits the extent of collaboration with foreign institutes and companies. It will be interesting to see if the major conglomerates will remain committed to biotechnology or if they will reevaluate their investments in this area as did some of their Japanese counterparts. Also, though it has made progress towards democratization, South Korea has a volatile political situation. Political instability leading to street riots and industrial strikes would have a negative effect on the buildup of the science base and on the investment in new technologies such as biotechnology.

TAIWAN

Government

In May of 1979, the Taiwan government initiated a "Ten Year Science and Technology Development Plan" to improve the nation's economic foundation, to increase the well-being of the people and to establish a self-sufficient national defense system. The ten year plan called for an increase in R&D in both the public and private sector. Historically, R&D in Taiwan has been mainly the responsibility of the government with the private sector

preferring to buy technology or to enter into licensing agreements with foreign firms. Therefore, the burden of financing R&D has fallen on the public sector. The government is trying to increase the percentage of the GNP spent in R&D to 2% by the end of this decade and at the same time to shift the cost of R&D to the private sector through the use of incentives and/or added taxes.

In 1982, a revised version of the plan was adopted in which eight key areas of science and technology were selected for special consideration. These areas were: energy, materials, information, automation, biotechnology, hepatitis control, electro-optics and food technology. With the adoption of this strategy, the National Science Council (NSC) of the Executive Yuan was charged with the promotion of biotechnology. Biotechnology was given special prominence because of the following reasons:

- most of the raw materials for the biotechnology industry are renewable
- it demands less energy consumption
- it requires a higher level of manpower resource
- capital investment is relatively small
- it causes less pollution
- it has wide applications in health care, agriculture, environmental protection, and energy industries.

(Biotechnology, 1988)

The strategy adopted to promote biotechnology was to attempt to integrate up-stream research, midstream development and downstream industrial production. Up-stream research is mainly conducted in the Institutes of the Academia Sinica, midstream research is assigned to the government initiated Development Center for Biotechnology, and down stream production is the responsibility of private companies.

The NSC is responsible for planning, funding and administration. With the Ministry of Education, NSC funds academic research and training. In addition, NSC is the major funding agency for basic R&D. Limitations of funds have led NSC to place priorities on the areas that are to be funded. In research, these include genetic engineering, hybridoma technology, tissue culture techniques, enzymology, fermentation and bioconversion. Priorities have also been established for development and industrial production. Program areas for development are pharmaceuticals, agriculture, specialty chemicals and environmental protection. Special emphasis is focused on the pharmaceutical, fermentation, and biotechnology industries.

The Council of Agriculture is another agency of the Executive Yuan with programs that have special emphasis on biotechnology. In 1987, a new plan was proposed to revitalize agriculture on Taiwan, with biotechnology as an important component. The areas

targeted in the plan include:

- development of new diagnostics for disease in animals
- use of biotechnology in horticulture
- use of gene transfer for the improvement of soybeans and other crops
- development of new methods for diagnosis and prevention of plant disease
- research into embryo transplants in animals
- application of biotechnology to aquaculture
- application of biotechnology to food processing

Universities and Research Institutes

Of the four countries covered in this study, Taiwan is the best endowed in the biological sciences. Laboratories in the national universities and research institutes, as well as laboratories in the medical centers and agricultural research stations provide a broad biological base. The most important of these are in the Chinese Academy of Sciences (Academia Sinica). In addition to the traditional research laboratories, the National Science Council established the Development Center for Biotechnology (DCB) to find commercial applications for new scientific discoveries.

The most prestigious of the Taiwanese universities is National Taiwan University (NTU). While its principal role is the teaching of undergraduates, there is also considerable research activity. The Department of Agricultural Chemistry is one of the better known departments at NTU. It takes in approximately 50 undergraduates a year and a similar number of graduates (mostly at the M.S. level). Research is primarily aimed at molecular biology, enzymology, improved plant strains, fermentation and food processing. The National Chung Hsing University located in Taichung (in the center of the island) also has a biotechnology oriented group, numbering less than forty. Research at this small university (enrollment of 3,000 compared to 18,000 at NTU) is primarily directed at plant and animal diseases. However, while there are active research projects at the universities and medical centers, the major effort in biological research is in the Institutes of the Academia Sinica.

In 1986 and 87, two new research institutes were established in the Academia Sinica. These were the Institute of Molecular Biology (IMB) at a cost of $3 million and the Institute of Biomedical Sciences (IBMS) at a cost of $4 million. In addition, the Institute of Botany had its facilities modernized.

The Institute of Molecular Biology has used a combination of tenure-track staff members and visiting professors who have chosen

to spend sabbaticals at the Institute. The directorship of IMB has been rotated among four of these visiting professors, all of them Americans of Chinese descent. The use of visiting scientists to provide scientific leadership to the various research groups is a creative attempt to compensate for the shortage of trained molecular biologists in Taiwan, and to provide the IMB with on-stream projects. The major research focus of the Institute is in the areas of cellular response to stress, molecular interactions, and genetic programming. In addition, a training program has been established in collaboration with National Tsing-Hua University and other universities. (Institute of Molecular Biology, 1988).

The Institute of Biomedical Sciences (IBMS) was first proposed in 1980 with the approval of the Council of Academia Sinica and the Office of the President. The Institute began research activities in 1986 with five professionals and a total staff of 23. The staff now exceeds two hundred including over forty scientists with the expectations of an additional thirty research scientists joining the staff this year. As in the case of IMB, extensive use is made of visiting scientists, primarily from the United States. One of the principal goals of the Institute is the advancement of diagnostic, therapeutic and preventive measures in cardiovascular, infectious, neoplastic and other diseases. Research activities are directed in the areas of

cardiovascular research, eicosanoids, neuroscience, cancer and virus, cell biology, and epidemiology and within the last year an increasing emphasis on the molecular approach to biomedical sciences such as molecular and cellular neurobiology, gene regulation, and cancer, molecular parasitology and molecular toxicology. IBMS collaborates closely with IMB and shares common facilities such as the library, electronics shop, machine shop, stockroom and auditorium. In addition, under the aegis of IBMS, three clinical research centers were established at the National Taiwan University Hospital, the Veterans General Hospital and the Tri-service General Hospital. (Institute of Biomedical Sciences, 1988).

The third major research institute involved in biotechnology is the Institute of Botany. Unlike IMB and IBMS, the Institute of Botany has a long standing history. In order to meet the growing demands for genetic engineering and molecular biology, an additional research building was constructed and opened in 1985. With the expansion in size, the Institute has proceeded to integrate the new biological methods into its research programs. Work in rice proteins, the rice genome, wheat germ lipase and anti-tumor agents head the list of projects. (Institute of Botany, 1988).

One other Institute worth noting as regards biotechnology is the Institute of Biological Chemistry. Established in the mid 70's with funds from the National Science Council, the Institute was located at the National Taiwan University and had a joint research agreement with its Graduate Institute of Biochemical Sciences. Initially, the institute had a long term program on biologically active proteins with special emphasis on snake venom proteins in the short term. These areas have been expanded to cover studies of growth hormone, prolactin and gonadotropin, the crystallins of the eye lens and enzymes at the level of both the protein and the gene. The interest in animal toxins continues but has shifted to hornetin, a lethal phosphatase A1 produced by certain hornets in Taiwan.

The Taiwan provincial government also supports a research institute, the Taiwan Agricultural Research Institute located near Chung Hsing University. Completed in 1977, the Institute is fairly modern, and is organized into six divisions: agronomy, horticulture, agricultural chemistry, plant pathology, applied zoology, and agricultural machinery. Some of the research projects are the development of rust resistant and salt-tolerant strains of soybean, increasing the protein content of sweet potatoes used for animal feed, studies of Chinese herbal medicines

and the characteristics of Stevia, a plant that contains a natural low-calorie sweetener.

DCB was established in 1984 with capital provided by the Taiwan Grain and Feeds Development Foundation and a group of biotechnology related private organizations. It is run as a non-profit organization with the mission to transfer technology from the academic sector to private industry, as well as to evaluate and acquire foreign technology. In addition, it tries to bring together foreign and Taiwanese companies to form joint ventures in biotechnology. DCB, located on the main campus of the National Taiwan University, has forty laboratories, a library, greenhouse, animal room and a pilot plant. Areas of research encompassing biotechnology include pharmaceuticals, pollution control, agricultural products and specialty chemicals. The Center is organized into seven technical divisions, one administrative division and a business division. DCB employs almost 240 people, 14% with doctoral degrees and 26% with master's degrees. The technical divisions are: molecular biology, biochemistry, microbiology, cell biology and immunology, applied chemistry, agricultural biotechnology, and process development. Altogether, they are working on over 35 projects including diagnostics (hepatitis, cancer and pregnancy), amino acid production by bioconversion, synthesis of biological pesticides and diagnostics

for animal disease to name a few. The projects can be generally divided into three categories; research, industry related R&D, and production. Funding comes from contracts from a variety of sources including the Ministry of Economic Affairs, the state-owned companies such as Taiwan Sugar Company and Chinese Petroleum and private companies, including Lifeguard Pharmaceuticals, Ve Wong Company and USI Far East Company. The broad research approach of DCB has raised criticism in some circles that the Center lacks focus, but a more serious shortfall has been the lack of visible success in technology transfer. (Biotechnology, 1988)

Industry and Finance

The state of biotechnology in the industrial sector in Taiwan is limited. The most important biotechnology-related companies are those in traditional fermentation and agricultural products such as the state-owned Taiwan Sugar Company and Taiwan Tobacco Company. The pharmaceutical industry is primarily involved in formulation, packaging, and marketing. The need to expand to high value-added products is becoming more important, however, as Taiwan enters the 1990's, with increasing labor costs and the rising value of the NT$. NSC analyzed the potential markets for new biotechnology-related products and estimated that a market

worth an estimated $807 million would be reached in the mid 1990's. As part of the government's decision to promote high technology in Taiwan, the Hsinchu Science-Based Industrial Park was created and placed under the administration of the NSC.

The Science-based Industrial Park is located 80 kilometers southwest of Taipei and occupies over 5,000 acres. Several institutes of higher education and research are located within the park including: National Tsinghua University, National Chiaotung University, and the Industrial Technology Research Institute. Any company that wishes to establish itself in the Park must fulfill several requirements including having a product(s) with potential for development and innovation, having an operation that will contribute to the economic reconstruction and national defense of Taiwan, and having a significant research department, to name but a few. Companies meeting the requirements are entitled to certain investment incentives such as low interest loans, tax incentives, waiver of duty on equipment, and, if they need venture capital, NSC may become its investment partner for up to 49% of total shares. The company may buy back any or all of the shares held by NSC. Foreign investments are accorded the same basic incentives as domestic investors with a government guarantee for twenty years against requisition or nationalization of any enterprises of which 45% of the shares are held by foreigners or overseas Chinese. The

science park currently employs over 16,000 people, in almost 100 companies, four of which are involved with biotechnology.

Lifeguard Pharmaceutical Company is one of the biotechnology related companies located at the Hsinchu Science-Based Industrial Park. It was established there in 1984 basically to produce Hepatitis B vaccine. Major share holders include the Executive Yuan Development Foundation, Bank of Communication, Central Investment Co., and DCB. Lifeguard was started with $6 Million in capitalization with equity distribution being 37% government, 13% government owned firms, and 49% private. While Lifeguard is associated with DCB, the technology it is utilizing to produce Hepatitis B vaccine was not derived from research at DCB. The plasma fractionation process was licensed from Pasteur Vaccins (France) and the plant was purchased from Sanofi (France). Lifeguard intends to use biotechnology to develop other pharmaceutical drugs, and in collaboration with DCB, they hope to develop a rDNA hepatitis vaccine.

General Biologicals, established in 1984, is also located at the Hsinchu Science-Based Industrial Park. Its purpose is to provide diagnostics, particularly for hepatitis. This company has an initial capital investment of $4 million raised from private concerns and government. General Biologicals has been on shaky ground because of charges of patent infringements in their

diagnostic kits. In addition, it is currently undergoing reorganization and a change of management. What effects these current events will have on the long term viability of the company remain to be seen.

An interesting company is Pan Labs which consists of research laboratories in Seattle, Washington and development laboratories in Taipei. Pan Labs provides three kinds of fermentation services: new product characterization, yield improvement, and enzymatic bioconversions to major client companies. Its product areas are: antibiotics, vitamins, amino acids, nucleotides, carbohydrates, and industrial enzymes.

Prosperity in Taiwan has resulted in the accumulation of a large amount of investment capital. Some of the major corporations such as China Petroleum and Formosa Plastics are capable of using their resources for diversification into new business sectors that might involve biotechnology. None of them has made any major investments in this direction. Companies looking for venture capital have several options depending on whether they choose to deal with the government or the private sector. The Industrial Development Agency in the Ministry of Economic Affairs is an excellent source of information and will assist in finding partners and financing. Furthermore, the Agency also determines whether the company qualifies as a "strategic

industry", a designation which makes a company eligible for numerous government incentives (see Table 6). Priority projects can receive direct funding from the government, either from the Development Fund of the Executive Yuan or the Bank of Communications. The average investment is in the range of $1-$5 million, but in special cases mezzanine financing of up to $20 million is also possible. To date there has been only one investment associated with biotechnology ($2 million in Health Care Investment Corp. [formerly Steinberg and Lyman Health Care Ventures] of the United States). One of the objectives of this investment was to gain access to technology and also to recruit U.S. companies for operations in Taiwan, however, so far no U.S. biotechnology companies have been attracted to Taiwan. In practice Health Care Investment Corp. has not invested outside of the United States.

In the case of government investment in a project, the company providing the technology can receive up to 15-20% of the equity in exchange for its technical contribution. This technology share can increase to 25% if the enterprise is located in the Hsinchu Science Park. There is no limit placed on technology share if the deal does not involve government funding. One of DCB's key roles is to match foreign companies with state owned Taiwanese firms with DCB receiving research contracts from

Table 6

TAIWAN'S "STRATEGIC INDUSTRIES" AND BIOTECHNOLOGY.

Criteria for "Strategic Industry"

High Technology Intensity
High Added Value
Large Market Potential
Large Economic Fringe Benefit
Low Energy Requirement
Low Pollution

Biotechnology related major "Strategic Industries"

1. Vaccines
2. Diagnostic reagents
3. Hormones
4. Antibiotics and amino acids produced by fermentation of bioconversion techniques
5. Enzyme products
6. Microbial reagents for pollution control
7. Biopesticides for agriculture
8. Plasma fractionation products
9. Monoclonal antibody products

Source: Industrial Development Bureau, MOEA, ROC, 1988.

the joint venture. No joint ventures have emerged yet from its efforts. It has been felt that the limitation of dealing only with state owned companies is too restrictive since such organizations tend to be bureaucratic and slow moving.

Venture capital is particularly strong in Taiwan with a number of important funds some of which are associated with U.S. venture capital organizations. Among others are: Hambrecht and Quist ($60 million); International Venture Capital Investment Corp. (part of the Walden Group, San Francisco), Ho-Tung Ventures, and China Venture Management Corp. There have been no major investments in biotechnology, but all of them are interested in companies requiring mezzanine financing. The preferred areas for investment are: medical instrumentation and devices, diagnostics, agriculture products, and food processing. (Hsu, 1988).

Summary

Of the four countries in this study Taiwan seems to have the most advantages. It has:

- an active government policy to promote biotechnology
- a well developed research establishment in the biological sciences
- a large pool of expatriates in the United States

- ample sources of investment capital.

However, the effective use of these assets still requires considerable effort. Government policy has developed a comprehensive plan that encompasses basic and applied research, technology transfer, and commercialization. The NSC plays an extremely important role in both supporting basic research and managing its integration into the economic development of the country. In some of these functions, it is very similar to EDB in Singapore, but it lacks the authority in economic matters that EDB enjoys. It is extremely difficult for the government to manage all of these steps in the application of a technology particularly as the private sector becomes increasingly important in finance and industry. Aside from hepatitis, Taiwan has found it difficult to identify other major project areas for industrial development and/or to find the key personnel to lead such efforts.

The research establishment in the biological sciences is one of the best developed in Asia, and is probably second only to Japan. This is further strengthened by the existence of a large pool of Taiwan scientists in the United States, many of which have been remarkably successful professionally. Taiwan has made effective use of such individuals as advisers and visiting scientists and in providing incentives for their return to the country. Molecular and cell biology have been introduced into a

large number of laboratories all over the country, and the training of scientists in such skills has become commonplace. Difficulties still remain in a shortage of senior scientists that are capable of directing and coordinating the various research efforts and in the continuing division between research and education. Research is still concentrated in the institutes with education being a function of the universities.

The industrial sector represents the weakest element in Taiwanese biotechnology. It lacks major companies involved in biotechnology, and lacks a significant number of new small biotechnology companies. The reasons for this are complex, but one major factor is the industrial profile of Taiwan which is based in small and medium firms. Most of these are manufacturing operations with a rapid turnover in goods and with no need for R&D or product development. The financial community is also conservative and not interested in businesses that have a major R&D component or a significant lag time in generating a product. Nevertheless, the markets in health care and agriculture do exist and are likely to be profitable ones, so one would expect to see the creation of new small firms probably as joint ventures with U.S. firms of the type seen in Singapore.

CONCLUSION

Opportunities and Obstacles for U.S. Firms

A. Potential Markets for New Biotechnology Products in Southeast Asia.

The rapid increase in purchasing power and the removal of many government restrictions that had been used to promote savings has led to a rapid growth in the markets of Southeast Asia. These markets are intrinsically different to those of the industrialized countries of the United States, Western Europe and Japan and center around human health care and agriculture.

Human health care: at present, the best opportunities are those related to public health (i.e., diseases and conditions that affect large numbers of people). At the top of the list are diagnostics and vaccines for the infectious diseases and ailments prevalent in the region (e.g., hepatitis, Dengue fever, sexually transmitted diseases). Antibiotics and nutrition products also command major markets in this region. A related area is instrumentation particularly as related to the automation of diagnostic products. Of particular importance is the fact that the use of radioactive products is extremely limiting, so whether

detection techniques are being applied to human or animal diagnostics or to the food industry, they should use non-radioactive labels.

Agriculture: agriculture is an important component of the economies of these countries and their neighbors. The agricultural sector includes the production of crops for domestic food consumption and products directed towards export markets (very often involving ornamentals and tropical fruits). One particular area of interest is in increasing productivity by the development of new strains with improved characteristics such as disease resistance, the ability to grow in different climatic regions, and higher yield. Another area is in improving the quality of high value added products such as flowers and exotic fruits so that they can meet the higher standards of developed countries. The indiscriminate use of chemicals in agriculture is opening up important new markets for alternative biological products as fertilizers and pest control agents.

Another important area is that of animal, poultry and fish breeding. As the Asian diet changes, there is an increasing demand for both meat and fish products. This requires improvements in animal health care and creates a demand for diagnostics and vaccines. Increased production and quality is creating a demand for such new rDNA products as growth hormones

and the introduction of transgenic animals and fish, and services such as embryo transfer. It must be remembered that fish and shellfish represent an important component of the Asian diet and that certain varieties (e.g., tiger prawns, abalone) command very high prices both in domestic and export markets.

Specialty chemicals: this sector has been closely related to food additives, e.g., aromas and flavorings, and there is a developing interest in genetically engineered products such as naturally derived food dyes and flavor enhancers. Some of these can also be used for the cosmetic industry.

Waste treatment: the lack of environmental controls and the rapid growth of industry and agriculture have resulted in seriously polluted environments in many of these countries. In the long term, there will be an increasing market for products and processes that will replace currently used chemicals and for waste treatment processes.

An important point is that the market for many of these products in these countries is price sensitive. While in the West, a product with leading edge technology can command a higher price, the same is not true in these countries. The consumer, whether a business executive or an ordinary citizen, will pay for a new product about the same price as for the old product it is replacing.

B. Strategies Available to U.S. Firms.

The strategy for a U.S. firm depends on the type of agreement it is looking for. These usually include: research, marketing, offshore manufacturing, licensing and joint ventures.

Research contracts: The cost of R&D in the United States is perceived as being too high, so small biotechnology companies are unlikely to receive research contracts unless the contracts are part of a larger agreement. With the expansion of R&D in countries such as Taiwan and Singapore, it may be more cost effective to contract out projects for products/processes of importance to the region to the local institutes and universities. The cost might be further lowered if the host government provides grants and/or tax incentives.

Marketing: Market rights for Asia usually do not include Japan and should be negotiated in that manner. The individual markets for products for human health care and agriculture is rapidly growing in South Korea, Taiwan and Singapore (while its domestic market is small, it is a major distribution point for the Southeast Asia region). Since individual markets are limited and can rapidly reach saturation, many companies develop an Asian strategy involving entry into one country followed by marketing into its neighbors (e.g., Singapore). The choice of the entry

market is dependent on the product and its market projections. The choice of the second stage markets requires a choice of whether it will involve the other NICs, LDCs or the large markets of China and Japan. Joint ventures also provide access to the markets of the United States and Western Europe.

Offshore manufacturing: In biotechnology offshore manufacturing is probably only appropriate for large and medium companies. One key factor is the package of government incentives that can effectively lower investment costs and local taxes and maximize profits. Labor costs are also an important element in choosing a site. Location is also sharply influenced by the existence of both tariff and non-tariff barriers for the export of certain products to neighboring countries.

Licensing: The opportunities for licensing seem to be fairly limited at this time because of the relatively small number of companies involved in biotechnology in these four countries. One possible mechanism is an initial marketing agreement with a trading corporation moving on to licensing if the market warrants it.

Joint ventures: The standard model for this type of agreement has the foreign partner providing capital and possibly land and/or the physical plant and the U.S. partner putting up its technology and possibly some matching investment. In exchange,

the U.S. company receives equity in the joint venture (these are known as technology shares). Foreign investment will usually come from large established companies/financial organizations and/or government development banks. Such projects require the existence of tangible product lines with defined markets. Such projects can be the beneficiaries of significant government incentives. Individual countries have restrictions on the maximum percentage of foreign ownership and of technology shares. In addition, there is also the possibility of reverse investment into the U.S. company in order to insure a continuing flow of technology transfer. There can also be an option for the foreign partner to roll over equity from the joint venture into the U.S. company.

C. Barriers Facing U.S. Firms Wanting to do Business in the Region.

1. Intellectual property rights: This is not a problem in Singapore while both South Korea and Taiwan have introduced new legislation (enforcement of which still remains to be tested) and there are serious problems in Thailand.

2. Non-tariff barriers involving regulations for pharmaceuticals and agricultural products (e.g., requiring retesting in each country) as well as lists of protected products.

3. Establishment of marketing networks: this is associated

with language and cultural problems. Most frequently it leads to a requirement for a local partner, which can also ease the way around difficulties with local corruption and nepotism.

4. Unwillingness to finance any major R&D component in a deal: this is partly associated with a desire to get rapid entry of a product into a market and assure a flow of revenue.

5. Shortages of manpower at technical and managerial levels particularly when there is a requirement for international experience.

6. Cultural differences in conducting business.

7. Living conditions for expatriates: if an agreement requires the stationing of foreign technical or managerial staff abroad, the site determines the cost and feasibility of moving expatriates and their families to that location.

Asian Strategies

A. Factors to be Considered with Respect to Japan, China and the NICs.

1. The commercialization of biotechnology is at an early stage. This is particularly true for all the Asian countries except Japan. At the present time, the markets of Singapore, South Korea, Taiwan and Thailand have not yet been developed and

are wide open. The markets for new biotechnology products have not yet attracted the attention of companies from Japan or Western Europe (not to mention the Unite States). Early entry into such markets will assure future market share of what are likely to become highly profitable business areas. This represents an opportunity for U.S. biotechnology companies which are highly regarded as relates to their technology, but are suspect in terms of their having real products that can lead to reasonable cash flow.

2. As mentioned in the preceding section, an effective business strategy must take into account all of Asia. Though the term Pacific Rim has a certain resonance, it does not reflect the diversity of Asia which includes a large number of countries at different levels of development: industrialized (Japan), NICs, and LDCs. An important aspect of this is that the markets of Japan, the NICs, and possibly China, must be considered separately. The Japanese market is an exceedingly important one, but for political, commercial and cultural reasons it is an exceedingly laborious and expensive one in which to gain access. In the case of the NICs, the total market might be very attractive and the initial investment might be low, but the challenge is that of creating a regional market. China and the LDCs have serious problems of infrastructure, and the issue of gaining access to the

larger Asian markets and the lack of a convertible currency in these countries makes it necessary to factor in barter trading or offshore manufacturing.

3. The rapid economic growth of the NICs has resulted in increased purchasing power and the ability to finance major industrial/commercial initiatives. This does not mean that Asian investors and their money will easily part company, particularly when it comes to high technology projects with a high risk. They will be willing to finance R&D only if they already have cash flow from existing products.

4. The technology has to be adapted to meet both regional needs and pricing structures (consumer is tightly attuned to prices; preferably same price, better product). While U.S. biotechnology companies and their products have attracted the most attention, this does not mean that the United States has a monopoly on such technologies, and they will encounter increasing competition from their European and Japanese counterparts. It must be emphasized that the United States does start out with the advantage that many of the scientists and managers in these Asian countries have been U.S. trained and are familiar with U.S. firms and products.

5. There is a well developed regional business network that in a number of key countries centers around the Chinese business

community, and this network can be used effectively to expand operations into the region.

6. The United States has the largest pool of foreign scientists in the biological sciences. Many of them come from Asian countries (e.g. Taiwan, Hong Kong, China [PRC], Korea). Recruitment of such individuals by U.S. companies in order to carry out technical and commercial projects in Asia would be an intelligent use of human resources.

7. A crucial factor is the package of government tax and fiscal incentives and grants/subsidies that can maximize profits and minimize investment costs. This is subject very often to case by case negotiation with the government involved. Government involvement also helps in insuring protection of intellectual property violations.

8. Activities in Asia should insure protection of intellectual property or be so designed as to minimize the risk. This can be done by getting foreign government involvement or have the foreign partner (preferably a large institution) be the lead investor.

B. Options for the U.S. Government in Promoting Activities.

If the United States is serious about promoting biotechnology as a major industrial technology, it should develop a minimum

government strategy which in the case of these four countries would involve the following points:

1. The United States embassies should regularly monitor the situation as relates to intellectual property with appropriate action in cases of serious violation. The same should be done with non-tariff barriers.

2. The U.S. Foreign Commercial Service should develop greater expertise in high technology industries including biotechnology. Their commercial sections abroad should identify the opportunities for U.S. biotechnology companies and also provide assistance to them when trying to establish new businesses in the Asian countries.

3. Act to get harmonization of regulations for new biotechnology products in the Asian countries particularly in the area of pharmaceuticals and genetically engineered plants and animals.

4. Promote regional conferences and workshops focusing on technical developments of commercial significance which would enable the exchange of information and establishment of personal contacts. Hopefully, these would be the first step towards working agreements between the United States and foreign firms.

5. Develop a network of organizations that can provide support and guidance to U.S. biotechnology companies doing

business in these countries for the first time. Such a network would include federal government agencies such as Department of Commerce, U.S. Trade and Development Program, Department of State, state offices of international trade, and trade associations such as the Association of Biotechnology Companies and the Industrial Biotechnology Association.

6. Work with USAID and international development agencies to promote the application of biotechnology to public health and agriculture in the LDCs. This should provide opportunities for U.S. biotechnology companies in contract research, sales and joint ventures.

C. Options Available to Private Sector.

1. Once having identified Asia as a market, the U.S. company has to make a long term commitment and maintain a presence there even though it might not be profitable in the short term.

2. Given the cultural differences, care must be taken in selecting personnel for overseas assignments, and insure that they will be active there for an extended period due to the importance of personal relationships in doing business.

3. The U.S. company must do its homework in familiarizing itself with the activities of its potential partners, including the foreign government.

4. It is essential to become familiar with the pricing structures of each market and cost projects accordingly.

5. Business in these countries requires a long term view requiring a great deal of patience, extensive travel, and a great deal of face to face negotiations.

Appendix A: Acronyms used in this report.

ADB - Asian Development Bank

AIDS - Autoimmune Deficiency Syndrome

ASEAN - Association of Southeast Asian Nations

BVP - Business Venture Promotion

DCB - Development Center for Biotechnology

EDB - Singapore Economic Development Board

GNP - gross national product

IMB - Institute of Molecular Biology

IMBS - Institute of Biomedical Sciences

IMCB - Institute for Molecular and Cell Biology

INIT - Initiatives in New Technology

KAIST - Korean Advance Institute of Science and Technology

KDIC - Korea Development Investment Company

KOGERA - Korea Genetic Engineering Research Association

KORCAG - Korea Research Council for Applied Genetics

KOSEF - Korea Science and Engineering Foundation

KTFC - Korea Technology Finance Corporation

LDC - lesser developed country

MOST - Ministry of Science and Technology

MOSTE - Ministry of Science, Technology and Energy

NCGEB - National Center for Genetic Engineering and Biotechnology

NICs - newly industrializing countries

NPI - Native Plants Inc.

NSC - National Science Council

NTU - National Taiwan University

NUS - National University of Singapore

PATH - Program for Appropriate Technology in Health

PDAS - Product Development Assistance Scheme

PPD - Primary Production Department

PRC - People's Republic of China

RDAS - Research and Development Assistance Scheme

rDNA - recombinant DNA

SEAVI - Southeast Asian Venture Investments

STDB - Science and Technology Development Board

TAVC - Thailand Agribusiness Venture Company

USAID - U.S. Agency for International Development

VCC - Venture Capital Company Ltd.

WHO - World Health Organization

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COMMERCIAL BIOTECHNOLOGY IN JAPAN

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INTRODUCTION

This is a descriptive assessment of commercial biotechnology development in Japan. Advances on the part of Japanese biotechnology, and Japanese skill in commercializing that which they and others have developed, promise to initiate a new era in R&D and product development for the industry at large. Part A provides an overview. Part B and C provide descriptions of biotechnology applications in different industries.

PART A. JAPANESE BIOTECHNOLOGY: OVERVIEW

Biotechnology has crept into a wide range of industries, and shown signs of maturing into a basic technology. Fine chemicals, foods, agricultural feed, seedlings, and other products have emerged in the growing repertoire of biotechnology-related goods. Biotechnology is now becoming an integrated part of the pharmaceutical industry. Many in the industry have come to regard biotechnology an essential "tool" for drug research and development.

The 1988 market for products using gene manipulation and cell splicing increased by 72% over the previous year, expanding to Y62 billion in Japan.[1] When products of cell cultivation are added, the total comes to approximately Y77 billion. The 1989 biomarket may well reach Y100 billion, over Y200 billion if related industries are included. Our estimate of total biotechnology R&D in Japan was about $2.3 billion in 1987.

[1] Nikkei Biotechnology, Nikkei Bio Nenkan 88/89 (Nikkei BP, Tokyo, 1988).

JAPAN'S 1988 BIOMARKET

Product	Sales (in billions of Yen)
(Gene Manipulation)	
Human Insulin (recombinant)	3.3
Growth Hormone (recombinant)	8.5
Alpha Interferon	1.5
Hepatitis B Vaccine	2.0
Diagnostic Enzymes	0.01
Tryptophan	1.5
Restriction Endonuclease (recombinant)	0.2-0.3
Industrial Enzymes	0.4-0.5
Detergents	10.0
Total	27.6 (1987 = 11.0)
(Cell Fusion)	
Monoclonal Antibody External Diagnostics	25.0
Chlorella "Marine Omega A", "Marine A"	0.04
Herbicide "Meiji Herbi Ace"	3.0
Fermentation & Brewing	2.7
Wine (Fusion Bio A = Y0.75 billion)	6.0
Bread	0.01+
Total	34.4 (1987 = 25.0)
Gene Manipulation + Cell Fusion	62.0
(Cell Culture)	
Urokinase	2.5
Beta Interferon	7.0
Alpha Interferon	5.5
Cell-Cultured Korean Ginseng Food Products	0.01+
Total	15.0 (1987 = 13.3)
Total Bio Products	77.0

Source: Nikkei Biotechnology Nenkan 1988/89

Japan's 1989 Japanese government "Bio-Budget" increased Y12 billion from 1988, to Y83.7 billion.[3] This includes expenditures by all the government's major ministries and departments. While the Bio-Budget has grown markedly over the past 5 years, it should be clearly noted that changes in the scope and makeup of the biotechnology industry itself make comparisons to the past difficult.

Bio Budgets for 1985-1989
(in billions of Yen)

Budget Year	1989	1988	1987	1986	1985
Total	83.7	71.7/53.1	45.6/39.9	36/22.4*	17.7*
MITI	7.6	5.7	5.8	5.4	4.1
MoA,F&F	7.4	6.6/3.6	3.2	3.1	2.2
MHW	35.7	31.1/15.7	12.1/5.0	3.4	2.6
STA	18.2	13.8	10.6/12.0	10.3	8.6
MoE	14.4	14.0	13.6	13.6	...
Environment Agency (EA)	0.34	0.34/0.1	0.1	0.1	0.05
MoC	0.11	0.15	0.16	0.13	0.1
Min. of Labor	0	0.01	0.01	0.01	0

/: is used in cases where budget definitions have been changed from previous years. The figure to the left is the budget under the definitions of the previous year, and the figure to the right is the budget as defined in the current year
*: MoE budget not included
Source: Nikkei Biotechnology, 3/13/89

[3] Bio Intelligence, 3/13/89.

Percentage Increase/Decrease in Yearly Bio Budgets 1985-1989

Budget Year	89/88	88/87	87/86	86/85
Total Avg.	+17%	+16%	+11%	+27%
MITI	+33%	-2%	+7%	+32%
MoA,F&F	+12%	+13%	+3%	+41%
MHW	+15%	+30%	+47%	+31%
STA	+32%	+30%	+17%	+20%
MoE	+3%	+3%	same	...
EA	same	same	same	+100%
MoC	-24%	slight -	-23%	-30%
MoL	-100%	same	same	first year

Bio Budget +/- ratios are calculated for budgets of consistent composition
Source: Nikkei Biotechnology 3/13/89

Biotechnology is now utilized in a variety of sectors, including: pharmaceuticals, fine chemicals, diagnostic drugs, food products, agriculture, fishery, environmental purification, cosmetics, and others. These application of biotechnology often overlap, causing problems in classification and regulation for both government and the private sector. For example, recent advances in nutrition science as well as in life science are contributing to a convergence of the pharmaceutical industry and the food processing industry. A similar industrial integration due to biotechnology can be observed between the cosmetic industry and the pharmaceutical industry.

Both government and private industry have demonstrated a commitment to competitiveness in biotechnology that should produce

significant developments. Biotechnology has been one of the few high-tech fields in which the US and Europe have maintained their lead in R&D as well as in commercialization, but Japanese government and industry have been quick to learn and respond to developments in the West. Expansion of Japanese technological expertise seems destined to bring about structural change that will put Japanese biotechnology on a par with the West, altering the dynamic of international competition.

R&D Size: $2.3 Billion[3]

Due to the rather ambiguous definition of biotechnology used in Japan (and elsewhere), an exact estimate of the biotechnology research market is difficult to provide. Japanese government statistics concerning a rather broad "life science," which includes new biotechnology as well as conventional research in animals and medicine, provides an upper bound estimate for biotechnology R&D. Statistics for "rDNA R&D," which is only a fraction of today's new biotechnology R&D, will provide a lower bound estimate for biotechnology research. The Japanese government's biotechnology budget also provides insights to help estimate the total biotechnology R&D in Japan. Using these statistics, our estimate for the total biotechnology R&D in Japan in 1987 is approximately $2.3 billion, which was about one half of the total U.S. R&D in

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[3] This section is based on Aki Yoshikawa, "Japan's Biotechnology R&D," BRIE, University of California, Berkeley, 1988.

biotechnology. .

Expenditure of Life Science R&D by Purpose
(Eight Categories, 100 million yen)

Purpose	1982	1983	1984	1985	1986
Life Science: Total					
Total	6492	7426	7840	8838	9179
Industry	2944	3348	3709	4285	4361
Research Institutes	840	859	985	1110	1232
Universities	2707	3220	3147	3444	3587
(1) Elucidation of vital Phenomena and biotic functions					
Total	613	729	680	776	850
Industry	37	47	51	58	93
Research Institutes	47	62	53	68	85
Universities	530	620	576	650	672
(2) Experimental animals					
Total	200	208	202	226	231
Industry	73	69	67	85	99
Research Institutes	29	23	25	27	29
Universities	98	116	110	114	102
(3) Health and medicine					
Total	4505	5286	5562	6266	6324
Industry	2338	2702	2931	3384	3331
Research Institutes	340	354	417	473	474
Universities	1827	2229	2214	2409	2519
(4) Environmental preservation					
Total	268	272	312	378	397
Industry	67	65	69	94	98
Research Institutes	128	129	158	187	203
Universities	72	77	85	96	96

Continues

Continued

Purpose	1982	1983	1984	1985	1986
(5) Utilization of organisms & their functions for mining & manufacturing.					
Total	224	256	339	386	445
Industry	178	208	278	315	367
Research Institutes	27	26	39	44	52
Universities	18	21	22	26	27
(6) Food resources					
Total	447	458	517	576	670
Industry	213	221	251	300	320
Research Institutes	198	197	217	225	291
Universities	36	40	48	52	59
(7) Utilization of biotic energy					
Total	73	63	71	67	68
Industry	26	23	32	32	26
Research Institutes	34	24	25	25	31
Universities	13	15	14	11	11
(8) Other life science					
Total	161	155	158	163	195
Industry	12	11	28	17	27
Research Institutes	36	43	51	59	68
Universities	113	101	78	87	100

Life Science R&D in Japan

Life Science R&D -- Total

Purpose	1983	1984	1985	1986	1987
Number of organizations conducting life science R&D	1163	1212	1291	3141	1403
Number of researchers	95647	107600	108802	115880	121345
of which Genetic Engineering	2041	2755	3304	4219	4934
Internal R&D expenditure (MY)	649217	742646	784043	883833	917909
of which Genetic Engineering	12847	19888	24712	36206	43651
Contracted R&D expenditure (MY)	41369	45157	50935	55246	61931
R&D expenditure/researcher (10K)	1053	1049	1090	1159	1142
R&D expenditure/ researcher of genetic engineering	1107	1446	1327	1591	1572

Life Science R&D -- Industry

Purpose	1983	1984	1985	1986	1987
Number of organizations conducting life science R&D	307	330	354	362	381
Number of researchers	24472	25940	27811	29495	30991
of which Genetic Engineering	658	1024	1236	1462	1768
Internal R&D expenditure (MY)	294448	334801	370887	428454	436093
of which Genetic Engineering	7926	12930	13742	19266	25164
Contracted R&D expenditure (MY)	35519	38760	42463	45885	53419
R&D expenditure/researcher (10K)	2373	2448	2476	2666	2512
R&D expenditure/ researcher of genetic engineering	1746	2085	1678	2063	2294

Life Science R&D -- Research Institutes

Purpose	1983	1984	1985	1986	1987
Number of organizations conducting life science R&D	341	345	370	403	423
Number of researchers	11278	11543	12235	13104	14743
of which Genetic Engineering	270	329	382	580	657
Internal R&D expenditure (MY)	84019	85887	98480	110973	123150
of which Genetic Engineering	1920	2642	4511	8820	8700
Contracted R&D expenditure (MY)	4954	5364	7591	8446	7733
R&D expenditure/researcher (10K)	1625	1636	1770	1880	1834
R&D expenditure/ researcher of genetic engineering	1613	1773	2685	3366	2959

Continued.

Life Science R&D -- University

Purpose	1983	1984	1985	1986	1987
Number of organizations conducting life science R&D	515	537	567	576	599
Number of researchers	59897	70117	68756	73281	75611
of which Genetic Engineering	113	1402	1686	2177	2509
Internal R&D expenditure (MY)	270750	321957	314677	344405	358666
of which Genetic Engineering	3001	4316	6458	8120	9787
Contracted R&D expenditure (MY)	886	1033	881	915	779
R&D expenditure/researcher (10K)	614	621	612	635	637
R&D expenditure/ researcher of genetic engineering	510	712	738	753	707

Changing Attitude Toward Biotechnology

Many Japanese executives in biotechnology-related industries stress that biotechnology is quickly moving from a nascent to a mature, basic technology.[4] Our assessment trip to Japan revealed more reserved and "realistic" expectations on the part of Japanese executives toward biotechnology. Their reservations at least partially reflect their disappointment with the less than spectacular effectiveness of first and second generation biotechnology drugs, such as interferon and TPA.

[4] The Japan 1989 BioIndustry survey by Nikkei Biotechnology, entitled "From Dream to Reality - The melding of fields as technology is actualized" (5/8/89). Nikkei sent out 604 survey forms, receiving 419 responses, and published results of the survey in the 5/22 edition of "Bio-Intelligence."

Biotechnology booms in the early 1980s, often referred to as "Biotechnology Fever," drew companies from across the industrial spectrum into biotechnology R&D and commercialization, and the market for bio-products generated through biotechnology and peripheral industries has already reached approximately Y200 billion. Biotechnology has quickly come of age, assuming its position as an essential technology.

On the other hand, the initial "high fever" period for biotechnology has already passed in Japan. The technology is no longer the darling of economic planners, but is recognized as just another processing technology or a "tool" in drug development, albeit an important one for future expansion. Some companies show signs of shrinking their overstretched efforts in biotechnology R&D to concentrate on their fields of specialization. The age of multifaceted biotechnology would seem to be coming to an end.

Changing Views Toward American Biotechnology Entrepreneurs

Today, rDNA and cell fusion techniques have already been established as the basis of biotechnology. Many major integrated pharmaceutical companies, such as Merck and Squibb, routinely use these techniques as research "tools." Biotechnology is no longer a monopolized expertise of smaller entrepreneurial biotechnology specializing companies, but has become a routine tool in the pharmaceutical industry.

The fact that biotechnology is now a mere "tool" in the well established pharmaceutical industry symbolizes the unavoidable destiny of biotechnology. Biotechnology is a process technology, and there is no such thing as a "biotechnology industry." Unlike the semiconductor technology which created a new product and an entirely new category of industry, biotechnology will not create such a distinctive new industrial category. Biotechnology will realize its maximum commercial impact through integration with existing industrial experience. If a firm tries to develop a biotechnology drug, it needs to understand the business and economics of pharmaceutical companies. In this regard, biotechnology companies are in essence baby pharmaceutical companies, baby food processing companies, and baby chemical companies, etc., who are striving to become individuals in each industrial target. They must grow and experience growing pains to survive.

In the early stages of biotechnology development, Japanese companies aggressively acquired American biotechnology know-how. Between the years 1981 and 1986, there were 71 collaborative ventures in biotechnology between American and Japanese companies. Most of this collaboration took the form of technology licensing from American companies to the Japanese. During the same period there were only 6 cooperative efforts with French companies, and 9

projects with English companies. In this regard, research in many biotechnology companies in the U.S. has been, in essence, financed by Japanese yen.

In the early 1980s, many biotechnology companies competed in studying the effective medical use of physiologically active proteins of human origins. It became apparent, however, that many of these proteins achieved less than speculated medical effectiveness. Many earlier "super" biotechnology drugs developed by entrepreneurial biotechnology companies reached their high point in mass media publications and in hopeful investors minds.

Even though biotechnology-specializing companies are still playing and will continue to play an important and innovative role in the advancement of biotechnology, the changing dynamics of technology and capital required for research are pushing larger established pharmaceutical companies, such as Merck and Ciba Geigy, to the center of biotechnology research.

Japanese companies are very sensitive to these changes in the biotechnology environment. They have distinctly different attitudes toward American biotechnology start-up companies today. The Japanese disposition towards biotechnology entrepreneurs, or more generally biotechnology itself in the early 1980s, could be characterized as a fever. However, today there is a more reserved,

rather cynical attitude toward "California style" biotechnology entrepreneurs.

Many Japanese executives, especially those in established pharmaceutical companies, view biotechnology companies as merely a phenomenon of the technological transition of the past. First generation biotechnology techniques are now routine tools. Although in the initial stages of the biotechnology race, entrepreneurs could create a start-up company with a small amount of capital, today's biotechnology research is becoming more costly and capital intensive which is suited to larger companies. Many Japanese firms don't believe that American biotechnology companies, even the most well-known and well publicized ones, can grow to become integrated pharmaceutical makers.

Industrial Application in Japan: Diversified

Biotechnology in Japan is characterized by a wide range of industries involved in research and marketing of bio-related products. Even though the pharmaceutical application of biotechnology attracts the most mass media attention, food processors are the largest group involved in biotechnology, primarily because even medium and smaller companies in this field have felt the need to grapple with this new technology. Pharmaceutical companies in Japan have begun to commercialize various biotechnology drugs, but many of these originate in European

and American laboratories.

Companies Responding to Nikkei Biotechnology Survey (By Industry)

Industry	Number of Companies Using Biotechnology
Total	419
Food Processing	91
Pharmaceuticals	77
Chemicals	77
Electronics/Appliances	42
Agriculture/Animal Husbandry	37
Construction/Plant Engineering	26
Textiles/Pulp	18
Trading Companies	17
Mining/Oil/Energy	12
Research Institutes	11
Steel and Non-Ferrous Metals	10
Other	42

Source: Bio-Intelligence (Nikkei Biotechnology, 5/8/89).

Japanese companies entered the biotechnology field in the greatest numbers in two peak periods, one in 1982, the first "bio boom," and the other in 1985. Quickest to enter, by industrial sector, were trading companies, textile makers, pharmaceutical companies, rubber and glass makers, alcohol and food processors, and chemical industries, in that order.[3] These sectors, although individual corporations sometimes deviate, account for Japan's first bio boom. The second boom came with the entry of electronics and appliances, construction, agriculture - marine bio - animal

[3] Nikkei Biotechnology, op.cit.

husbandry, steel and other metals, and mining - oil - energy.

Biotechnology "Majority Peak"* for Various Industrial Sectors

Sector	Majority Peak	Ratio of Companies
Trading Co.s	1980	3/6
Textiles/Pulp	1982	4/6
Pharmaceuticals	1982	21/40
Rubber/Glass	1982	2/4
Food Processing/Brewing	1983	29/56
Chemicals	1983	23/40
Electronics/Appliances	1984	14/25
Construction/Engineering	1984	9/18
Agriculture	1984	14/27
Steel/Non-Ferrous	1986	5/7
Mining/Oil/Energy	1986	6/8

*The Majority Peak is calculated by first determining the total number of companies in a given sector which entered into biotechnology research between 1976-1989. The Majority Peak year is the year in which the companies in any particular sector reached half or more of their total for the period. i.e.: if the total for 1976-1989 is 16 companies, then the Majority Peak year will be that year in which the total-to-date reaches 8 or more companies.

Source: Nikkei Biotechnology, 5/8/89.

Biotechnology has motivated companies to invest in high value added pharmaceutical products with which they were previously unfamiliar. Many companies have attempted to enter the

pharmaceutical market by utilizing biotechnology.[6] However, chemical, pharmaceutical, and food makers all showed less interest in diversification through biotechnology in 1989 than in 1985, preferring to move downstream in production instead, where they feel they better understand consumers. Relative newcomers like the construction and electric industries, on the other hand, show an increased interest in branching out through biotechnology. They have not yet fully explored the possibilities for their industries, and the great scope of the projects in which they are involved makes biotechnology a promising investment.

Biotechnology Diversification Ratio*

Sector	1985	1989	Trend
Chemicals	4.3	3.1	down
Pharmaceuticals	4.8	1.2	down
Food Processing	3.3	2.7	down
Agriculture@	2.8	0.7	down
Construction	2.6	5.5	up
Electronics	3.7	4.4	up

*The Biotechnology Diversification Ratio is defined as follows: Note: Number of companies in sector applying biotechnology outside their traditional business, Number of companies in sector applying biotechnology to their traditional business only.
@: Figure does not include fisheries
Source: Nikkei Biotechnology 5/8/89

[6] See Aki Yoshikawa, "The Other Drug War: U.S.-Japan Trade in Pharmaceuticals, California Management Review, University of California, Berkeley (Winter 1989), and Japanese Biotechnology: New Drugs - Industrial Organization, Innovation, and Strategic Alliances, BRIE Working Paper 33, University of California, Berkeley, January 1988).

Chemical companies have been most active in seeking to branch out into new fields, while pharmaceuticals and agricultural producers have been relatively passive investors but popular targets. Consequently, diversification has occurred primarily through the actions of aggressive industries like the energy sector, with its enormous capital resources. Food products and seed products have been other popular fields for experimentation by outsiders.

Preferred Diversification Sectors for Specific Industry Groups
(shown as % of companies within group interested in entry)

Target Sector	Industry Group: Chem.	Pharm.	Food	Agr.	Enrg.	Const.	Elec.
Pharm.	33.8	---	10.9	0.0	17.9	0.0	0.0
Diag.	27.2	---	11.8	2.4	3.6	0.0	2.9
Vet. drugs	5.2	0.0	0.9	0.0	7.1	0.0	2.9
Foods	23.3	6.3	---	2.4	17.9	3.6	8.8
Chem.	---	3.2	9.0	0.0	14.3	0.0	2.9
Agr. chem.	18.2	0.0	3.6	0.0	0.0	0.0	2.9
Seedlings	14.3	0.0	13.6	---	7.1	21.4	11.8
Animal husbandry	2.6	0.0	0.0	---	0.0	0.0	0.0
Marine	3.9	0.0	1.8	---	3.6	21.4	8.8
Envmnt	5.2	0.0	0.9	0.0	14.3	42.9	14.7
Const.	10.4	0.0	3.6	0.0	10.1	---	32.4
Reagents	10.4	14.2	10.9	0.0	14.3	0.0	0.0

Source: Nikkei Biotechnology 5/8/89

Japanese R&D expenditure for biotechnology has increased 80% since 1985, to approximately Y200 billion.[7] This figure, despite its phenomenal growth over the past decade, still represents only 3% of Japan's total yearly R&D budget. Bio R&D levelled off in 1988, changing little from the 1987 figure. Industry has pulled back from its frantic rush into every new possibility, to concentrate upon sectors with more concrete potential for commercialization.

Bio R&D Expenditure and Employees - Japan's Top Ten

1988 Bio R&D Expenditure (in billions of Yen)		1989 Researchers in Bio R&D	
1) Mitsubishi Chemical	16.9	1) Mitsui Toatsu Chem.	320
2) Kureha Chemical	4.0	2) Hayashibara Biochem.	198
3) Sumitomo Pharm.	3.5	3) Suntory	130
4) Mitsui Toatsu Chem.	3.0	4) Takara Shuzo	123
5) Meiji Milk	2.1	5) Tosoh Corp.	100
6) Indust. Protein Lab.	2.0	5) Toyobo	100
7) Hayashibara Biochem.	1.9	7) Kureha Chemical	80
8) Showa Denko	1.7	7) Chugai Pharmaceutical	80
9) NKK Corp.	1.5	9) Snow Brand	71
9) Sapporo Beer	1.5	10) Meiji Milk	70
9) Mitsubishi Petrochem.	1.5	10) Japan Tobacco Ind.	70

Source: Nikkei Biotechnology

However, with a more focused target, a 1989 survey shows 80% of respondents intend to increase their bio-research staff, while the majority also plan to establish new laboratory facilities.[8] While

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[7] Bio Intelligence, Nikkei Biotechnology (5/8/89), p. 4.

[8] Nikkei Biotechnology (5/8/89).

in 1985 electronics and appliance makers showed the most interest in new investments, rubber and glass led in 1989, followed by construction and metals.

Planned Expansion of Research Teams and Facilities - By Industry
(% of co.s within industry survey group indicating expansion plans)

Industry Group	Researchers (%)	Facilities (%)
Total (310 co.s)	79	46
Chemicals (61)	75	48
Pharmaceuticals (56)	82	45
Foods/Brewing (79)	82	43
Agriculture/Animal Husbandry (33)	73	33
Mining/Oil/Energy (11)	64	45
Glass/Rubber (5)	100	100
Steel/Non-Ferrous Metals (8)	100	63
Construction/Plant Eng. (25)	72	72
Electronics/Appliances (36)	64	28
Textiles/Pulp (14)	71	36
Trading Companies (7)	43	29
Information Services (4)	100	50
Institutes/Research Facilities (8)	63	50
Other (22)	73	36

Source: Nikkei Biotechnology 5/8/89.

Japanese bio-researchers, even conservatively estimated, now number over 10,000. Researchers studying recombinant gene technology in industry and academia account for only some 3,000 - 4,000 of these, indicating a wide range of exploration and experimentation.

Biotechnology in Japan: A Broad Concept

In a rush to introduce "bio-products" to the market, many companies have begun to use the "bio" label rather liberally. Definitions of what constitutes biotechnology have blurred, and confusion has appeared both among consumers and among producers.

The above mentioned survey found that although 110 companies reported total sales of commercial biotechnology at Y129.4 billion, actual biotechnology involving recombinant gene technology, cell fusion, and cell culture accounted for only Y26 billion of this figure. The remainder was comprised by peripheral industries such as bio plant and equipment (Y48 billion), and traditional "fermentation" technologies (Y55 billion).[9]

It is estimated the total 1988 Japanese market for products involving recombinant technology, cell fusion, and cell culture at Y77 billion.[10] Responses from industries developing monoclonal antibody-based diagnostics and industrial enzymes were incomplete, however, leaving some question as to the overall state of the market.

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[9] Ibid. p.7.

[10] Ibid.

The Japanese bio-market is at present balanced between cutting-edge technologies in genetic manipulation and peripheral supporting industries in plant, equipment, and others. As biotechnology matures into a key basic technology, Japanese companies have become polarized in their opinions about its applicability in the future. Numbers of companies feeling that biotechnology will have either a very limited or a very broad scope have both increased, while ambiguity about the future possibilities of the new technology has lessened. Industries at both ends of the spectrum seem to have reached a more realistic evaluation of biotechnology's role as a basic technology.

Grass-Roots Support

There is wide spread "grass-roots" public support for biotechnology in Japan. When the Japanese cosmetic company Kanebo introduced a biotechnology-based lipstick, widely publicized as a "biotechnology" lipstick, it proved a big commercial success. Another company, Kyowa Hakko, marketed a new "biotechnology" wine, called "Fusion Bio A." Japanese women are using biotechnology-based products on their lips, and Japanese men (and a growing number of Japanese women) are drinking biotechnology wine. I believe that Japanese people have a favorable attitude toward biotechnology-based products, and this may be the key to Japan's success in commercializing biotechnology. Thus various industrial applications of biotechnology may be pursued more rapidly in Japan than in the

U.S.

SECTORAL ANALYSIS

PART B: PHARMACEUTICAL BIOTECHNOLOGY

We explore the pharmaceutical industry in Japan in detail in this section, observing the actual impact of commercialization of biotechnology products. In Japan, the pharmaceutical industry is undergoing a structural and behavioral change initiated by the biotechnology revolution, particularly the efforts of non-pharmaceutical companies to enter the market through biotechnology.

B.1. Comparative Statistics of Japanese Drug Companies[11]

Japanese pharmaceutical firms are smaller than their U.S. and European counterparts. In 1985 the total sales of the 10 largest U.S. pharmaceutical firms was over $38 billion; it was about $12 billion in Japan. R&D spending by the top 10 American firms far surpasses that of Japanese firms in absolute value. The total R&D expenditure was $2,920 million for the 10 American firms, but only $976 million for the Japanese. Tables below presents the comparative statistics of the top 20 drug makers in the world in

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[11] Section B.1. and B.2. are based on Aki Yoshikawa, Multinationalization of Japan's Pharmaceutical Industry: Industry Observations and Theoretical Explanation, forthcoming Oxford University Press.

1985 and the top 10 Japanese pharmaceutical companies.

Compared with other leading drug makers in the world, Takeda is dramatically domestic; its overseas sales ratio is only 7 percent whereas the ratio was 98 percent for Ciba Geigy and was 36 percent for the relatively more domestic Merck. The average overseas sales ratio for top Japanese drug companies is approximately 5 percent whereas it is approximately 35 percent for American and is over 80 percent for European companies.[12]

[12] The difference in overseas sales ratios between European, Japanese, and American companies is partially due to the difference in degree of diversification and product mix.

World Top Pharmaceutical Companies in 1985
(million dollars, percent)

	Drug Sales	Total Sales	Ratio	Drug Sales	Overseas Ratio
1. Johnson & J.	4,214	6,421	66	2,431	38
2. A.H.P.	3,166	4,685	68	1,048	22
3. Bristol Meyers	2,985	4,444	67	1,314	30
4. Hoechst	2,878	17,430	17	13,025	75
5. Merck	2,824	3,548	80	1,272	36
6. Bayer	2,723	18,738	15	14,902	80
7. Ciba-Geigy	2,710	8,823	31	8,685	98
8. SKB	2,078	3,257	64	1,055	32
9. Pfizer	1,961	4,025	49	1,682	42
10. Sandoz	1,894	4,093	61	3,919	96
11. Warner-Lamb.	1,872	3,200	59	1,162	36
12. Abbott	1,866	3,360	56	1,047	31
13. Roche-Sapac	1,838	4,329	43	4,201	97
14. Lilly	1,786	3,271	55	1,171	36
15. Glaxo	1,689	2,056	82	1,346	65
16. UpJohn	1,593	2,009	79	676	34
17. Boehringer-Ing.	1,573	1,848	85	1,459	79
18. Takeda	1,555	2,741	57	182	7
19. ICI	1,363	15,612	9	15,177	97
20. Squibb	1,197	2,042	59	829	41

Source: Aki Yoshikawa, "Multinationalization in Japan's Pharmaceutical INdustry: Industry Observations and Theoretical Explanations," (1989).

Top Japanese Pharmaceutical Companies in 1986
(billion yen, percent)

	Drug Sales	Total Sales	Drug Ratio	Export Sales	Ratio
1. Takeda	309.2	492.6	62.8	28.9	5.9
2. Sankyo	234.1	279.7	83.7	4.5	1.6
3. Fujisawa	149.2	172.7	86.4	10.9	6.3
4. Shionogi	177.0	200.2	88.4	1.5	0.7
5. Tanabe	147.1	159.2	92.4	25.7	16.1
6. Eisai	130.3	150.5	86.6	8.1	5.4
7. Yamanouch	135.3	140.6	96.2	N.A.	N.A.
8. Daiichi	129.0	130.6	98.8	6.9	5.3
9. Chugai	102.7	108.9	94.3	3.5	3.2
10. Dainippon	71.7	83.2	86.2	N.A.	N.A.
11. Nip. Shin	34.4	41.1	83.8	N.A.	N.A.

Source: Yoshikawa (1989), Ibid.

Isolated Domestic Market

The Japanese pharmaceutical market is the second largest in the world, and was worth about $ 25 billion in 1985. The existence of a large Japanese domestic market, in addition to Japanese companies' inability to innovate break-through new drugs in the past explains Japanese companies' "passive" attitudes toward multinationalization in comparison with European companies (especially is comparison with the three companies in Switzerland, where the domestic market is extremely small). In terms of quantity, pharmaceutical imports exceed exports in Japan. In 1985, Japanese imports of pharmaceutical totaled 310 billion yen, whereas exports amounted to only 93 billion yen. As opposed to Japan's deficit in the pharmaceutical trade, the U.S. has been realizing a surplus, which

in 1986 was $764 million. In short, pharmaceuticals are one of the few high-technology products in which the U.S. is experiencing a favorable trade balance and Japan is not.

In Japan, companies in the automobile and the semiconductor industries have adopted aggressive export strategies to promote industrial growth. According to conventional wisdom, Japanese companies "created" a comparative cost advantage by mass-producing standard products and shifting downward across their long term average cost curve. However, unlike the automobile and semiconductor industries, exports represent only a small fraction of Japan's pharmaceutical output. Unlike the automobile and semiconductor industry, scale merit is rather trivial in pharmaceutical production. Competition in the pharmaceutical industry centered around innovation and the introduction of new drugs, rather than competition over price.

Strategic Shift in the Mid 1970s

In the early years of its industrial development, Japan depended heavily on the transfer of technology from abroad. Like other Japanese industries, the pharmaceutical industry imported crucial technologies and perfected them. Japanese drug companies licensed various new drugs innovated by foreign companies, performed clinical testings in Japan, and commercialized the drugs in Japan. Often the best selling drug in a Japanese drug company was a

licensed drug from abroad; thus, Japanese companies put their strategic emphasis on the marketing of these products. Competition centered around obtaining a license from a foreign company and marketing it effectively.

In the mid 1970s, Japanese firms realized the potential risk of their dependency on imported technologies. This risk involved the potential for the decision by a foreign licensor to market drugs directly in Japan instead of licensing to a Japanese company in. Companies also realized that in the future the ability to innovate a new drug would be more crucial for survival than marketing ability. Since Japanese companies shifted their strategic emphasis toward more R&D, R&D spending in Japanese companies has increased dramatically.

Between 1961 and 1980, 353 new drugs were introduced in the U.S. market; only 155 new drugs were introduced by Japanese firms. However the Japanese efforts in R&D began showing some positive results in the early 1980s. Japanese firms introduced 60 new drugs between 1981 and 1985, whereas American firms introduced only 51.[13]

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[13] However there may be a bias in this comparison since many new drugs developed by Japanese firms are originally licensed from foreign sources. The statistics showing the location of the discovering firm's home office instead of the location of the research or introduction of the drug may be more appropriate. Temin, op. cit., p. 145.

B.2. Dynamic Structural Changes in Japan's Pharmaceutical Industry

Several factors are promoting dynamic structural changes in the Japanese pharmaceutical industry through an increasing level of competitive pressure: (1) Massive entries of firms investing in biotechnology, (2) Decisions by foreign pharmaceutical makers to discontinue their sales tie-up arrangements with Japanese firms and to enter the Japanese market directly; and (3) the government policy to cut the NHI price to enhance innovative pressures. Structural realignment caused by these factors may bring about profound changes in the behavior of Japanese pharmaceutical companies.

Below factors affecting the industrial structure of the pharmaceutical industry and implications on industrial structure and performance are presented.[14]

New Domestic Rivals: Biotechnology

Today many Japanese non-pharmaceutical firms are attempting to enter the market through biotechnology. Non-pharmaceutical companies, food-processing companies such as Suntory and Ajinomoto, and chemical companies such as Mitsubishi Kasei Chemical and Asahi Chemical are major players in Japanese bio-pharmaceutical development. Among 170 firms that have joined Japan's biotechnology industry association (BIDEC), more than half are traditionally

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[14] The following discussions were originally presented at Yoshikawa, op.cit.

non-pharmaceutical companies. Even though some major chemical and food-processing firms in the U.S. have also tried to enter the pharmaceutical market, the extent to which this is occurring is much more limited in the U.S.

How much competitive pressure can these new entrants to the pharmaceutical industry generate? These new entrants have no know-how in drug development (e.g., conducting clinical testing), and no close contact with customers (doctors and hospitals). They just began their aggressive entries a few years ago, yet it takes as long as ten years to develop and introduce a new drug to market. Do established drug makers recognize these new entrants as competitors? Assessment of new domestic entrants by top executives of established drug companies differ substantially. Even though the competitive threat to existing pharmaceutical companies is still a "potential" rather than a reality, the massive entries of large domestic chemical and food processing companies have certainly generated a higher level of competitive pressure in Japan's domestic pharmaceutical market.

Challenge from Foreign Companies

There recently occurred a crucial change in Japan's regulation of the commercial relationship between foreign and domestic firms. Today, foreign firms can apply more direct, flexible, and aggressive strategies to the Japanese market. Japanese firms now face a more

direct foreign challenge in the domestic market, and unlike their new domestic rivals, the challenge from foreign companies is the reality today.[15]

Recently, many foreign firms in Japan have begun discontinuing their licensing to Japanese firms and are attempting to focus on direct investment (manufacturing of finished products and marketing). For example, Ciba Geigy discontinued its sales tie-up with Japanese companies when the firm recently decided to market its product directly instead of licensing it to Japanese companies.[16] Merck & Co. took a more aggressive measure to enter the Japanese market. The firm acquired Banyu Pharmaceutical, which was one of Japan's top pharmaceutical companies. With the acquisition of Banyu, Merck obtained hundreds of drug detail-men and their contacts.

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[15] Although none were in the top 100 in Japan (in terms of declared income), foreign drug companies enjoyed growth rates much higher than foreign-owned firms in other industries and higher than Japanese pharmaceutical firms. Some major foreign pharmaceutical and chemical companies, such as Bayer and Du Pont, also have established basic R&D facilities in Japan. In 1986 Upjohn announced its plan to establish a full-scale pharmaceutical research laboratory employing 400 researchers. Ciba-Geigy announced a similar plan.

[16] Fujisawa suffered greatly when Ciba-Geigy decided to discontinue their sales tie-up arrangement, which was worth 12,000 million yen a year to Fujisawa. Takeda's sales also declined when their tie-up with Ciba-Geigy was suspended.

Reduction in NHI price

Even though in principle firms can market drugs when they earn both approvals and licenses from the Japanese government, their actual sales depend on reimbursement under the National Health Insurance (NHI) scheme, which covers nearly all the Japanese population. Reimbursement prices are determined by the Ministry of Health and Welfare (MHW) according to guidelines established by the Central Social Insurance Medical Council (Chuikyo). A prescription drug cannot be marketed unless its price is listed under the NHI system.

The difference between the NHI price and the physicians' purchasing price is called the "doctor's margin," and is considered a source of income for medical doctors in Japan. Pharmaceutical makers have strong incentives to cut their prices so that physicians will prescribe their drugs. Competition among Japanese pharmaceutical makers to cut prices below the established NHI prices increases the unpredictability of profits.

Between 1980 and 1986, NHI pricing was cut by 44%, drastically squeezing the profits of pharmaceutical companies. The decision to lower NHI prices reflected the government's efforts to cut the "doctor's margin" because it was essentially a government subsidy to physicians. It also reflected the government's efforts to lower expenses in the face of a tremendous budget deficit. As a result of such a reduction in reimbursement price, many pharmaceutical

companies, especially small and medium sized drug makers, faced financial difficulties.

Some argued that reducing reimbursement prices would hinder firms' incentive to innovate. However, although NHI prices have been cut, MHW pricing has been more favorable for new drugs. Japanese pharmaceutical companies' strategy is, therefore, to innovate products under the assumption that new products receive more favorable reimbursement prices. Thus NHI's policy to cut prices promoted innovative efforts; the firm that can innovate is the one that can survive.

Synthesis

Decisions by foreign pharmaceutical makers to discontinue their sales tie-up arrangements with Japanese firms and to enter the Japanese market directly and, to a lesser degree, massive entries of firms investing in biotechnology, are causing dynamic strategic changes in the pharmaceutical industry. The government policy to cut the NHI price further enhanced competitive pressures.

One additional effect of the growing competitive pressure on Japan's pharmaceutical companies is their increasing attention to the global market. The cut in NHI prices also promoted a more global perspective. Increasingly R&D intensive (and probably larger as a result of the industrial reorganization), Japanese drug companies may find it both feasible and profitable to go abroad.

Japanese Drug Companies' Effort to Multinationalize[17]

I will present my casual observations and elaborate on the most likely scenario for a Japanese drug company to enter a foreign market (e.g., the U.S. market).

Although multinational Japanese automobile and electronics companies entered the U.S. market initially with low value added models with low cost and later moved up to higher value added market segments, I don't believe this low-end-market entry strategy is a good strategic choice for a Japanese drug company, especially one that is struggling to develop a new drug. Even though today's expanding generic drug market provides an entry opportunity for a low-cost foreign company, I don't believe Japanese companies will attempt to enter the U.S. market as aggressive generic drug producers (e.g., through the acquisition of a generic drug maker).

The key to success for a Japanese drug company in the international drug business is the ability to introduce successful new drugs continuously. The generic drug business is fundamentally different from the R&D based prescription drug business not only in intensity of research but also in management. Diversifying to generic drugs may discourage researchers' efforts to innovate new

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[17] Aki Yoshikawa (1989).

drugs and may also create a risk of dividing its top managerial resources.

Japanese firms may acquire an American generic firm. (For example, Fujisawa acquired Lypho Med.) However, the aim of such an acquisition is probably not the generic drug business itself but to establish a sales network. Some Europeans also established their base in the U.S. marketing through such acquisitions.

As Japanese companies become accustomed to foreign markets, there will be less incentive to rely solely upon licensing. In fact many of them are forming joint ventures with their American partners. Since they lack experience and knowledge concerning foreign regulatory authorities and markets, they prefer to form a joint venture with a foreign partner who is familiar with the regulatory framework. As is the case of the joint venture between Fujisawa and Smith Kline, Japanese firms will attempt to acquire full control of such a joint venture after a period of time.

Japanese entry to the U.S. market is likely to be less spectacular than European drug companies. It is highly unlikely that Japanese companies will try to conduct unfriendly take overs as did Hoffmann LaRoche. Their success in the U.S. depends on several factors: whether they can innovate a new product, whether they can obtain FDA approval in a reasonable amount of time, whether they can

establish a reputation with medical professionals, whether they can successfully market the product, and whether they can come up with successors. The process of multinationalization is likely to be difficult and time consuming for Japanese drug companies.

B.3. Pharmaceutical Biotechnology Update

The Japanese market for biotechnology drugs is dominated by the following products: insulin, growth hormone, alpha interferon (IFN), and hepatitis b vaccine. Alpha interferon and hepatitis b vaccine, as well as insulin produced through a new process (proinsulin method), came on the market in 1988. Alpha interferon is Japan's first domestic bio drug, where all previous recombinant pharmaceuticals have been imported. The market for recombinant pharmaceuticals in Japan is expected to be Y17 billion in 1988, a near doubling of the previous year's Y9.3 billion.[18]

In Japan, due to the scarcity of AIDS infection, the focus of biotechnology has been drugs to treat senility, osteoporosis and other bone diseases of aging, and circulatory diseases like myocardial infarction.

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[18] Nikkei Biotechnology

R&D Infrastructure

In 1986, The Ministry of Health established the Human Science Foundation to support domestic development of new drugs. In 1987, using surplus money from the drug poisoning relief fund, the "Health Sciences Related Industries Financing System" was set up to promote development of pharmaceuticals and medical equipment.

In 1988 the system invested in two companies: DDS Labs[19] (seven private companies including Asahi Chemical and Ajinomoto; development of a drug delivery system using glucose carrier) and the Biosensor Research Lab (four companies including Kuraray, Chugai, and others; development of a medical sensor using photo-electronics). Total investment and financing was Y1.3 billion for 1988.

The Japanese Koseisho (Ministry of Health and Welfare) awarded U.S.'s Genentech a grant to study a rare hereditary disease that causes premature aging. The grant was awarded to study Werner's Syndrome. Genentech scientists are searching for the gene that causes the disorder in the hopes of finding clues about the aging process and developing treatments for diseases associated with old age. The grant was the first to awarded to a foreign company by the

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[19] Faced with difficulties in first and second generation biotechnology drugs - 1) short in-blood half-life, 2) multiple functionality, 3) location specific effectiveness, and 4) limits of injection induction - drug delivery systems (DDS) have attracted increasing attention.

Ministry of Health. Genentech scientists and Japanese scientists will study Japanese families affected by the disease.

Genentech will have exclusive worldwide rights to products that result from the Koseisho sponsored collaborative research project. We believe that this grant reflects a more open policy toward international research collaboration on the part of the Ministry of Health. This cooperation will help Genentech toward its effort to gain access to Japan's collection of data on the rare disease. The ultimate challenge to Genentech is to establish a system to realize effective feedback from research in Japan and to integrate this research at its headquarters in South San Francisco.

Takeda Pharmaceutical took an unusual step in offering funds to Harvard University, and will soon be establishing an endowment. This will be the first Japanese endowment for biotechnology-related research outside of Japan. Both Suntory (Rockefeller Univ.) and Hitachi Chemical (UC Irvine) have supported basic biological research in America, but this support has not taken the form of endowments.

Japan's Shiseido, the largest Japanese cosmetic company, made an $85 million pledge to the Massachusetts General Hospital and Harvard University to establish a new skin research center. The ten year project will aim at basic dermatology: effects of light on

skin, cell differentiation, immunology, and biology of skin pigments. Under the agreement, Shiseido can only enjoy two seats in the center's eight member scientific board and has no specific say over research. Harvard will hold patents from the research and receive royalties. However, Shiseido has the first right to an exclusive license.

Commercial Development

Currently in Japan, clinical testing is being carried out on 15 varieties of bio drugs (11 in 1987) in a total of 43 test cases (39 in 1987). When Dai Nippon Pharmaceutical's interleukin (IL) is included that total comes to 16 varieties in 44 cases, a sizeable increase in new prospective pharmaceuticals over last year.

New drugs entering clinical testing recently include: granulocyte colony stimulating factor (GCSF), human monoclonal antibodies (anti-viral, bacterial shock treatment), mouse monoclonal antibodies (anti-cancer), natural gamma IFN, insulin inducer (monomeric), IL1 beta inducer, IL6, granulocyte macrophage colony stimulating factor, blood coagulation factor VIII, epidermal growth factor (recombinant, urea extract already available), and human monoclonal antibodies (anti-cancer). Among them, those that have completed clinical testing and applied to the Ministry of Health for production approval in 1988 included: interleukin 2 (Shionogi), TPA (Asahi Chemical, Mitsubishi Chemical-Kyowa Hakko), EPA, second

generation hepatitis b vaccine (Osaka Microbiological Research Institute), and first generation hepatitis b vaccine (Green Cross).

Toray, a textile company, and its pharmaceutical partner Daiichi Pharmaceutical, jointly introduced **Feron**. Although it was initially approved for cancer treatment in August 1986, the drug was also approved for the treatment of hepatitis B. Hepatitis B treatment now accounts for more than 50 percent of its sales. In its first year of sales, Feron earned 78.3 billion yen ($65 million).

Sumiferon is an alpha interferon introduced by Sumitomo Pharmaceutical in April, 1987 with technology transferred from Wellcome (England). It is regarded as the first "biotechnology" drug on the Japanese market, although it was manufactured through the cell cultivation method rather than actual genetic engineering.

Takeda, using technology transferred from Hoffmann-LaRoche, introduced an alpha interferon, the first genetically engineered drug produced domestically in Japan, in January 1988. It was marketed by both Takeda (**Canferon**) and by Japan Roche (**Roferon**). In its first five months in the market place, its sales exceeded 500 million yen (approximately Y424 million of CFN-A and Y103 million of Roferon).

Hoffmann-LaRoche's main rival in the U.S. market, Schering-

Plough, introduced its alpha interferon, Intron A, to the Japanese market about the same time. It was imported by Essex and marketed by both Essex and Yamanouchi.

Japanese Interferon Sales (wholesale)
(million yen)

Year	1987								
Month	1	2	3	4	5	6	7	8	9
Feron Daiichi	356	453	665	627	549	527	635	630	563
Feron Toray Medical	26	36	85	85	75	69	83	73	95
Sumiferon				98	295	388	427	387	407
Canferon A									
Roferon A									
Intron A Essex									
Intron A Yamanouchi									

				1988				
	10	11	12	1	2	3	4	5
Feron Daiichi	748	627	619	424	456	359	458	385
Feron Toray Medical	112	95	96	60	67	44	62	50
Sumiferon	429	425	510	363	393	397	532	482
Canferon A				12	86	127	156	143
Roferon A				0	18	26	34	35
Intron A Essex				0	2	6	12	10
Intron A Yamanouchi				1	6	15	31	27

Shionogi has finished clinical testing of interleukin 2 (IL2), and has sought approval from the Ministry of Health. Shionogi used technology introduced from America's Biogen in the development of

the new product, which is targeted at kidney cancer. Shionogi is currently involved in a patent dispute with Ajinomoto over IL2.

Shionogi's gamma interferon was also approved for the treatment of kidney cancer in Japan. Takeda, Japan Roche, Toray, Daiichi Pharmaceutical, and Kyowa Hakko were all involved in the development of recombinant gamma interferon, but abandoned it as it too closely resembled existing alpha and beta interferon. Otsuka Pharmaceutical, too, is currently carrying out clinical tests on gamma interferon produced through the Hayashibara method.

In a related development, Suntory has received approval for a gamma IFN useful in treating skin cancer. Mochida Pharmaceutical, meanwhile, is marketing a cancer-treating beta IFN produced through fibroplast culture. Other developments include Kirin Beer's G-CSF which has just completed clinical testing.

In Japan, drugs currently approved for the treatment of hepatitis B are: alpha interferon from Japan Roche, Takeda, and Sumitomo; and beta interferon from Toray. Roche and Takeda use recombinant E-coli in production, while Sumitomo and Toray use cultured animal cells.

AIDS pharmaceutical development will be carried out, over a five year period beginning in 1988, through the Human Science

Foundation. The Foundation's first budget has been allocated Y300 million. Development efforts will target drugs to treat the AIDS virus itself, as well as medicines for various AIDS-related symptoms.

Clinical testing as well as commercialization of monoclonal antibodies are expected to increase rapidly in Japan. Teijin has developed a monoclonal antibody to the cytomegalovirus, and Takeda introduced from America's Centocor Co. a monoclonal antibody for external toxins (used in treating bacterial shock).

Toyo Jozo began clinical tests to develop a hormonal treatment for osteoporosis. Further, Teijin and Chugai have synthesized many vitamin d inducers in an attempt to develop a medicine for the same disease.

Asahi Chemical applied to the Ministry of Health for production approval for TPA in 1988. Mitsui Chemical-Kyowa Hakko soon followed, applying for approval of recombinant TPA. Chugai Pharmaceutical and Kirin Beer are expected to apply for production approval for recombinant EPO in 1989.

PART C. OTHER INDUSTRIAL APPLICATIONS

C.1. DIAGNOSTICS

Yearly production of diagnostic drugs is rising sharply. 1987's production figure (including imports) was Y189.5 billion, a yearly increase rate of 37.7%. Yet diagnostics make up only a small 2.98% of total pharmaceutical production.[20] Imported diagnostic drugs have flooded the Japanese market with the help of price competitiveness through the high yen and the standardization of regulations for diagnostic drugs stemming from the MOSS agreement.

In June, 1988 Teijin teamed up with Switzerland's Ares Serono Co., introducing 30 diagnostic drugs from Serono all at once, in an attempt to expand the company's presence in the diagnostic business. Nichirei, too, has applied for import approval for 30 varieties of monoclonal antibody diagnostics from BioGenex. According to the MOSS agreement, response must come within six months of application, facilitating integrated production planning.

1988 saw the introduction of 80 new monoclonal antibody products, bringing to 222 the total number available. Current applicants and projected developments should easily bring the figure to 300 in 1989. The current market size is estimated to be Y25

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[20] Diagnostic drugs are characterized by a high import-ratio, with imports growing to Y108.1 billion in 1987, increasing 65.5% from the Y65.3 billion imported in 1986. Domestic production in 1987 was Y81.4 billion, surpassed by imports for the first time.

billion.

Green Cross has proceeded to phase III of its testing diagnostic drug used in the diagnosis of intestinal cancer. The drug, obtained from the French Department of Nuclear Energy, is based upon monoclonal antibodies. Teijin, meanwhile, had reached phase III of clinical testing of an imaging diagnostic antibody for malignant melanoma introduced from America's Hybritech when it was forced to terminate development due to Hybritech's abandonment of the project. The company shifted, in 1988, to development of monoclonal antibody imaging diagnosis technology for rectal cancer. The Daiichi Radio Isotope Laboratory began clinical testing of diagnostic imaging technology for myocardial infarction using a monoclonal antibody introduced from Centocor Co.

In spring 1988 Toray became the first Japanese company to apply for import approval for a nucleo-acid probe-based diagnostic, a kit developed by America's Life Technologies Co. to detect papilloma virus on cervical cell samples.

Development of DNA probes in Japan accelerated in 1988, with the progression of linkages like Chugai Pharmaceutical-GenProbe (US) and Mitsubishi Petrochemical-Digene (US). Toyobo, too, was preparing clinical tests of a DNA probe targeted at viral and cellular diagnostics.

Technology has now emerged for direct use of DNA probes in the detection and diagnosis of human genetic disease and cancerous tissue. Referred to as genetic diagnostics, this technology is likely to open new fields of evaluation and treatment. The US has had genetic diagnostic labs since 1986, but in Japan the front runners - Special Reference Laboratory (SRL; a subsidiary of Fuji Rebio) and Shionogi began genetic diagnostics in 1987. By 1988 Otsuka Assei had opened a research institute, and all of Japan's major labs were equipped for genetic diagnostics. SRL set up a genetic diagnosis division in 1988, embarking in earnest upon genetic testing.

The Japanese market for home pregnancy tests, which grew to 500,000 units in 1987, hit a plateau in 1988, with sales figures virtually unchanged. At Y3,000 per unit, this brings total market value for the product to Y1.5 billion. 1987 brought a rush of monoclonal antibody-based products, but development has quieted down in 1988. Toshin Chemical aborted plans to import a pregnancy test drug from Israel's Teva Pharmaceutical, switching instead to a product from Quidel Co. of the US.

In Japan home pregnancy tests are classified as prescription drugs and cannot marketed as over-the-counter products. Their inability to advertise is a substantial marketing liability, and this has stifled the growth and distribution of the product. The

National Pharmaceutical Retailers Association, an organization of the country's small retailers, has applied aggressively for reclassification of pregnancy tests as marketable general medicines.

Pharmaceutical companies see the possibility of using genetic diagnosis to determine the constitution of the individual patient; particularly susceptibility to heart disease, cancer, and the like. They are targeting a future in which progress in genetic diagnostic technology will provide for rationalized preventative and health care services tailored to the individual through the use of genetic information.

The Biosensor Laboratories Co. Ltd., established through the joint efforts of Chugai Pharmaceutical, Hamamatsu Photonics, etc., and funded through R&D promotional support by the Ministry of Health, has been concentrating its activities on the development of receptor and gene probe technology to measure hormones.

C.2. FOOD PRODUCTS

Tissue culture, cell fusion, and recombinant gene technology are all applied in the food processing industry in Japan. New developments introduced the power of biotechnology to food processing, but growth within the industry was limited by jurisdictional power struggles among bureaucrats.

Tissue culture, particularly of ginseng, made substantial progress in 1988. Extract of ginseng, first tank-cultured by Nitto Denko has been added to a range of products, including "Chojusen," a wine introduced by Kikkoman, and "Royal Family," a health drink produced by a joint venture between Japan Tobacco Industries and Yoshitomi Pharmaceutical. Nitto Electric, in May 1989, introduced ginseng tofu to Mitsukoshi (a major department store chain) in Tokyo. Cultured ginseng has little odor or bitterness, making it suitable as an additive.

Kyowa Hakko introduced "Fusion Bio A," a wine made with yeast cultured through cell fusion, in May, 1988. The product, being promoted as "biowine," was the first test case for consumer receptivity to bio-foods. Japanese media as well as consumers expressed favorable attitude toward the product.

A food importer began to import recombinant chymosin from Holland's Royal Gist-Brocades (RGB). The company will send samples to cheese makers for testing. The importer was already buying artificial enzyme from RGB at about one-third the cost of natural chymosin. The new recombinant technology should allow further cost reductions by producing chymosin through yeast. Japan has no regulations regarding recombinant chymosin, but the substance has already been approved in Switzerland.

It will take time, however, for cheese makers to get the Ministry of Health and Welfare (MHW) approval they need to make full use of the new technology. The producers fear consumer reaction, and need a speedy approval from the MHW to compete with foreign products already entering and threatening to flood the market.

The MHW's Food Health Survey Committee's Special Subcommittee on Biotechnology is proceeding with plans for certifying biotechnology-based food products. A group was formed this spring to establish production safety and evaluation regulations for recombinant products, and results should be available by 1990.

Nisshin Co. recently announced that it has succeeded in producing artificial cacao oil. Methodological tests were successful, but with current large harvests and low prices for natural cacao, production costs remain prohibitively high in comparison to natural methods. Fuji Seiyu was the first to develop the artificial oil being used in the process of making artificial cacao, but with current market conditions the future of production is unclear.

Nisshin Bio R&D Institute will also begin experimental production of "vegetable cheese," through enzyme induced hardening of soy milk, in September. The process involves the use of an enzyme for hardening soy protein in place of the chymosin enzyme used to emulsify milk. The enzyme was removed from a member of the

bacillus family 6 years ago at the National Genetic Research Institute.

Bureaucratic Power Struggle Over Functional Foods

This is the age not just of nutrients, but of functionality of food products. The Ministry of Health in 1988 targeted funds for strategic planning of research into functional food products, "kino shokuhin," food products with added nutritional value. The Ministry of Agriculture and Fisheries, too, began in 1988 a 5 year plan for "development of factor functional alteration technology within the food industry." The Ministry of Health has embarked upon an ambitious plan to promote highly functional foods, establishing a health food strategy lab and a new food products safety strategy lab.

Scientifically developed functional foods should eventually form a new health food market. Many large Japanese firms targeted the kino shokuhin market. Next year, at the earliest, the Ministry of Health will determine guidelines for highly functional foods. Such a clear regulatory framework is necessary in order to promote smooth development of kino shokuhin in Japan. The first foods to be recognized are expected to be: casein phosphopeptide (CPP), edible fiber, and fructo-oligosaccharides.

A jurisdictional power struggle has broken out within the

Ministry of Health over control of regulation of functional foods. The controversy hinges on whether these will be considered food products or pharmaceuticals.

The Food Health Bureau presented a list of "functional foods" which the Pharmaceutical Bureau then reclassified as "health-oriented pharmaceuticals." Both bureaus recognize the huge potential market in "self-care" products, and insist upon jurisdiction over this newly important area.

The Pharmaceutical Bureau, citing the "dangers" of altered functional foods, opposes the products as they now stand (under the jurisdiction of the food health bureau). The Pharmaceutical division has gone so far as to suggest that functional foods should be flavored and packaged like medicine so that consumers will not confuse them with standard food products. The Pharmaceutical Bureau wants to include functional foods in the OTC drugs category, which, although not included in national health expenses, accounts for Y700 billion per year. The Food Health Bureau is hoping to justify its jurisdiction over functional foods through the 12th clause of the Nutrient Fortification Law of 1952, which states that with the approval of the Minister of Health, fortified foods may have their medicinal function and properties stated on the label. The Pharmaceutical Bureau has determined to fight the action. Jurisdictional confusion within the MHW has brought instability to

the whole field of functional foods.

The problems with regard to functional foods are the following:[21]

1) Proof of effectiveness - How far to carry clinical tests and experimental trials, how to examine the interaction of active and non-active ingredients, how to account for individual difference, and how to account for preventative effectiveness.

2) Proof of safety - What level of testing to carry out, and how to account for latent or long-term harmfulness.

3) Regulation and funding - Functional foods have a less obvious effect than pharmaceuticals, and testing and evaluation will require a prolonged process. If this process is funded entirely by the private sector, costs will skyrocket, and the government needs to consider burden-sharing and tax breaks in development.

4) Responsibility and Liability - If these products are approved by the government, how will the government respond in case of accidents?

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[21] According to Nikkei Biotechnology's Bio-Intelligence publication of 7/3/89.

C.3. AGRICULTURE BIOTECHNOLOGY

Japan has yet no research bodies examining recombinant plant products through field tests. This may imply that technological development in agricultural biotechnology is lagging in agricultural biotechnology in Japan.

The clerical work required to integrate planning differences between the Ministry of Agriculture and Fisheries and the Department of Science and Technology, necessary for environmental testing, has been slow. The Ministry of Agriculture and Fisheries plans to publicize guidelines for environmental release sometime in 1988. Recombinant plants should appear in the fields of Japan by 1990.

Seedlings

In 1988 tank-cultured, high-speed, mass-produced seedlings were offered on the market. One example was Mitsui Petrochemical's "Whitey." The same company also tank cultured and marketed miniroses. In 1988 Kirin Beer succeeded in tank mass-culture of the F1 rice embryo, and announced prospects for synthetic seeds. Although the seeds cannot at present be spread directly to the fields, the technology is now sufficient to combine them with tank-cultured embryo processes to mass produce seedlings.

Gakushu Kenkyusha (Gakken) Co. began direct mail marketing of wasabi (Japanese horseradish) seedlings to Japanese farmers. The

company introduced three new varieties, and is now waiting for registration from the Ministry of Agriculture, Forestry, and Fisheries. The new, high yield/virus-resistant varieties, two of Mizu Wasabi and one of Oka Wasabi, are being sold 200 seedlings to a bundle at a cost of approximately Y100,000. The seedlings can be quickly cultivated and their number increased thanks to enzyme immunity bred into the plants to make them resistant to the virus which presents the greatest obstacle in the cultivation of wasabi.

Gene Bank

The Ministry of Agriculture and Fisheries established a Gene Bank, which has distributed 25,000 varieties of seeds since opening in Tsukuba in January, 1986. The Bank was established to provide a strong base for the collection and distribution of useful plants and microorganisms.

The Ministry of Agriculture and Fisheries reports that in the period 4/88 to 3/89 it had 239 requests, and distributed 5,745 varieties through the Bank.[22] National research centers comprised the largest single beneficiary group, presenting 107 requests for 3,419 varieties. Foreign requests were second, at 42 for 1,309 varieties, followed by industry and farm cooperatives (64 requests for 735 varieties), universities (19 requests for 229 varieties),

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[22] Nikkei Biotechnology (6/5/89)

and public research institutes (7 requests for 53 varieties).[23]

Private industry, farm cooperatives, and agricultural high-schools tended to request rice varieties, 363 cases in all. Major corporate users were Kirin Beer, Kikkoman, Chugai Pharmaceutical, Mitsui Toatsu Chemical, Toa Nenryo, and Nippon Sekiyu.[24]

Distribution of Plant Genetic Resources 1/25/86 - 3/31/89

Overall Distribution

Type	Percentage
Total	100% (25,369 varieties)
Wheat	35%
Beans	28%
Rice	17%
Feed Grains, etc.	12%
Vegetables	8%

Distribution to Private Sector and Farm Cooperatives

Type	Percentage
Total	100% (1,510 varieties)
Rice	49%
Vegetables	20%
Feed Grains, etc.	19%
Wheat	7%
Beans	2.5%
Potatoes	1.3%

Source: Nikkei Biotechnology 6/5/89

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[23] Ibid.

[24] Ibid.

Other Developments

Kyowa Hakko, Sumitomo Trading Co., and America's NPI on March 17 formed BIONKS, a joint venture with the right to production and marketing of NPI's full line of plant-bio technology. BIONKS will market improved useful breeds, plant gene mapping, and useful microorganisms like VA bacillus. The new deal solidifies Kyowa Hakko's presence in the plant-bio business in Japan.

Kyowa Hakko's newly established Tsukuba Research Lab is expected to be a center for plant-bio research, and a resource for BIONKS. Capitalized at Y99 million, BIONKS is owned 45% by Kyowa Hakko, 45% by NPI, and 10% by Sumitomo Trading.

Mitsui group's main basic plant-bio research unit, Mitsui Plant-Bio Research Laboratories, has agreed to rent an open experimental laboratory ($47m^2 \times 6$) and an office ($30m^2$) in Tsukuba's Research Technology Center.

The Tsukuba center is a third sector enterprise conceived by MITI as a research core and supported by the Japan Development Bank, Mitsui Trading Co., and others. Facilities at the center are extensive, and Mitsui Plant-Bio joins a growing number of companies already located therein.

C.4. FINE CHEMICALS

Laundry Detergent

In 1988 Novo Seikagaku (subsidiary of Denmark's Novo Industri) began commercial production in Hokkaido of detergent enzyme "lipase" (for the dissolution of fats). The company achieved significant cost reductions in the revolutionary new process, which involves genetic alteration of aspergillus, a bacteria used in brewing alcohol.

Lion Corp. introduced "High Top," a laundry detergent using the recombinant lipase produced by Novo. The product sold better than expected, raising hopes for a large potential market.

Dishwasher Soap

Dishwashers have thus far had a limited appeal in Japan, partially due to their inability to clean the stubborn residue of Japanese glutinous rice. Enzymes produced through biotechnology may well provide soaps that solve the problem, however, and appliance makers are eager to see this new market opened up.

SCC Ltd., a joint venture between Shell and Daiichi Kogyo Seiyaku, first used an enzyme detergent to enter the market for dishwasher soap in 1986. In fall, 1987, Lion, at the request of Sharp, which had commercialized a compact dishwasher, began

production of a liquid enzyme dishwasher soap. Enzymes used in these new soaps include amylase (a starch solvent) and protease (a protein solvent). Amylase is particularly effective in breaking down rice residue.

Japan's current market for dishwasher soap is only Y500 million, but is expected to increase quickly with the spread of the dishwasher. If 50% of Japanese households were to own a dishwasher (roughly the ratio in the US), the soap market could jump to Y100 billion yearly.[25] With the ordinary soap market only Y60 billion yearly, this is an attractive prospect to soap manufacturers.[26]

Major Developers of Dishwasher Soap Enzymes

Company	Enzyme Type and Characteristics
Novo Co.	Amylase , Protease, Lipase
IBIS (Holland)	Alkali Protease, Amylase, Lipase
Showa Electric	Bacillus-Derived Alkali Protease (effective for fermentation at low temperature), Cellulase, Lipase
Toyobo	Neuter Heat-Resistant Protease, Amylase
Tosoh	Bacillus-Derived Heat-Resistant Alkali Protease
Daiwa Chemical	Bacillus-Derived, Heat-Resistant Alkali alpha Amylase

Source: Nikkei Biotechnology 5/22/89

[25] Nikkei Bio-Intelligence (5/22/89)

[26] Ibid.

In a related development, recombinant DNA lipase may find its way into lipstick remover.

C.5. BIOCOSMETICS

Total Japanese cosmetics production for 1986 was Y1.144 trillion, a small increase of 4.2% from the previous year. 1987 is expected to have brought a tiny 0.3% increase to Y1.1477 trillion. Japan Kanebo has become the first company to introduce a "Biotechnology Lipstick," hoping to test market response to biotechnology-based products. The lipstick (utilizing a tissue culture technique) is not a "high-tech" biotechnology product, but could be categorized as an "image" product. Consumer response was positive, however, and some Japanese companies are now attempting to develop more "scientific" products.

In 1988 Shuuemura Cosmetics introduced a product using hyaluronic acid produced through fermentation. Hyaluronic acid is a product of Kyowa Hakko, and the group already has the "Hiro" line of beauty parlor specialty products and the Biogram Day/Night beauty formula.

Sansei (?) Pharmaceutical, in cooperation with Kobe University, has developed a skin whitening process using malt acid. This has been incorporated into a cream that appeared on the market in 1988.

C.6. MARINE BIO & ANIMAL HUSBANDRY

Government Support for Marine Bio

MITI solidified its support for marine biology in 1988. The Ministry oversaw the establishment of third sector-style open research centers in cooperation with Japan Steel in Kamaishi city of Iwate Prefecture and Toa Nenryo in Shimizu city of Shizuoka Prefecture. Research companies set up by private industry will use the centers for marine biology R&D. NEDO, the New Energy Development Organization, will facilitate funding of this project.

The Fisheries Division of the Ministry of Agriculture, Forestry and Fisheries, faced with difficulties arising from the strengthening of 200 mile territorial waters regulations and low fish prices, is attempting to revitalize its role through effective use of available territorial water zones. To this end the Division will initiate the Marino-Frontier Project (to develop technology for the effective utilization of underdeveloped marine resources) in 1989. Marino-Forum 21, a five year technology development program, will have as its primary goal actualization of the project. The theme of the forum will focus upon technology easily utilized by the food industry. The amount of financing requested for the first year from industries is Y123 million, and the subsidy rate is 50%.

Development

Companies like Japan Steel and Japan Iron Pipe are targeting their obsolete factory space for use in marine biology. In 1987 Ishikawajima Harima Heavy Industries succeeded, through a subsidiary's marine biology, in developing technology for the mass breeding of kelp in Hokkaido. The product was sold as spices and animal feeds.

Using the most practical chromosome engineering technology available, Hitachi Ship Building in March 1988 came out with all female flounder. With the exception of the all female rainbow trout already in use in Hokkaido, this is the first commercialized all-female fish in Japan. "High tech" fish like an all-female and triple-size sweetfish should soon appear.

Kyowa Hakko, Nippon Gene, Earth Pharmaceutical, Toa Nenryo, Taiyo Fisheries, and others are using gene manipulation to develop fish growth hormones, a technology likely to change the face of the aquaculture industry.

Kyowa Hakko's Marine Research has succeeded, with a growth hormone made from recombinant E-coli bacteria, in promoting growth in a variety of fish: eels, sweetfish, sea bream, halibut, and others. This new development allows hormones to be introduced through food rather than injection or other inconvenient methods,

and brings practical use closer to actualization. Further testing of methodology and side effects is needed before commercialization of the technology.

Major Fish Growth Hormones at a Glance

Fish Type	Hormone producer	Characteristics
Abalone	Hokuri University	GH substance from abalone kidney
Sturgeon	Hokuri University Kyowa Hakko	90% amino acid
Cod	Hokuri University	187 amino acid
Tuna	Taiyo Fisheries	E-Coli recombinant GH
Striped Mackerel	Nippon Gene Mie University	Clone cDNA

Source: Nikkei Biotechnology 4/10/89

Triple sized sweetfish, created through gene manipulation, will be released into Japan's rivers this fall. This will be the first time such an experiment has been carried out, and actual testing has been delayed by fears that non-reproducing triple-size sweetfish will disturb the mating and procreative habits of their natural cousins. Officials fear that by mating with normal fish, the sterile sweetfish will ultimately reduce the natural population.

The projected testing, to be carried out in Gunma and Gifu Prefectures by the Marine Resource Preservation Association (a corporate entity), will help provide data to determine marine

biotechnology guidelines.

C.7. BIOTECHNOLOGY ANIMALS

Beef

In order to commercialize fertilized egg transplant technology, the Ministry of Agriculture and Fisheries provided funding, pressing for dissemination of technology, and calves born of transplanted fertilized eggs have appeared in all ranching areas.

Snow Brand and the prefectural research institutes have the lead in this area, but Meiji Milk, Nisshin Flour Milling, and Koiwai Ranching are also developing technology.

Transgenic Animals

In 1988 many varieties of transgenic mice were achieved in Japan alone. They include: the hepatitis b virus gene (Cancer Research Lab, Kumamoto Univ.), DNA restoration enzyme gene (Cancer Research Lab), gamma IFN gene (Tokyo Univ.), IL2 gene (Tokai Univ.), IL5 gene (Kumamoto Univ.), adult T-cell leukemia virus (Tokyo, Kyoto Univ.), adenovirus E1A gene (Snow Brand), cancer gene (Osaka, Kumamoto, Tokyo Univ.).

In 1988 the Living Organism Special Industries Technology Promotion Organization, an external organ of the Ministry of Agriculture and Fisheries, along with Toso and Nisseiken formed the

joint venture NT to begin research on cultivating transgenic experimental animals.

C.8. BIOTECHNOLOGY INSTRUMENTATION

Japanese Human Genome Project and Its Hardware Development

Today many segments of the Japanese biotechnology R&D instrument market (such as DNA sequencer, DNA synthesizer, and peptide synthesizer) are dominated by California's Applied Biosystems (ABI). ABI has been very successful (and lucky[27]) in marketing and has established its reputation in Japan.

Many well-established Japanese companies, such as Hitachi, Fujitsu, Seiko, and Toso are entering the market. With their reputations in Japan (and thus reliability), some of them, especially Hitachi, will become the major competitors in the world biotechnology R&D instrument market in the future. Severe competition, especially with Japanese firms, will lower many prices.

The government of Japan has introduced a program to promote the development of instruments necessary in the sequencing of the human genome in the early 1980s. An initial effort to promote the mass-

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[27] ABI's explosive success in Japan in 1986-1987 was partially due to the Japanese government's decision to buy American-made research equipments to avoid trade conflicts with the U.S. Such pressure from abroad (Gaiatsu) still exists in Japan, and such a special procurement is likely to happen again.

reading of DNA-base sequences was started in 1981. The program was entitled, "Extraction, Analysis, and Synthesis of DNA," and the aim of the program was to encourage DNA study in Japan by organizing the resources available in universities, private companies, and government research institutes.

Various companies, such as Seiko Instruments, Fuji Photo, Toso, and Hitachi, were selected for the project and have received governmental support. Seiko developed a microchemical robot to carry out a series of chemical manipulations. Fuji Photo developed a machine for the manufacture of prepackaged acrylamide gel film, and Mitsui is developing computer software for DNA sequence analysis. (Fuji later abandoned the project since it decided that there was not enough market potential for the product. The company's decision to withdraw from a government project attracted disappointment as well as anger among participating scientists.) Hitachi has developed several instruments for sequencing analysis (automatic scanner in autoradiograph, DNA sequencer). Under the leadership of Riken (Institute of Physical and Chemical Research), companies are collaborating to develop the entire automatic sequencing system.

However, Japan's Science and Technology Agency recently retreated from its enthusiastic support of the project. Now Japan's Human Genome Project is financed on a minimal budget. Riken's

hardware project is extremely ill-financed, and scientists in Japan are widely embarrassed by the situation. Many believe that the project lost its initial velocity because: (1) Unlike Japan's MITI, the Science and Technology Agency (STA) has minimal bureaucratic prestige and little political power, rendering it unable to establish a large project, and (2) Bureaucrats in STA simply didn't understand the importance of the project. In general these assessments of STA by Japanese scientists are correct. However, it must be noted that Japanese scientists themselves are not involved in active policy making. The entire science and technology policy-making apparatus was at fault, and bears responsibility for the aborted genome project. In a few years, the Japanese government may arrange a new financial package for the genome project, as many foreign scientists, like their Japanese colleagues, express little confidence toward Japan's "black box" approach to science policy.

Tax Incentive for Equipment Purchases

The Japanese government offers tax incentives and conditional loans to encourage the purchase of equipment and facilities (depreciable assets) necessary for R&D, and hence to promote R&D in the private sector. Tax incentives and credits may be the most effective way to promote private R&D in biotechnology by the government. A firm can deduct from its corporate tax 20 percent of any R&D spending that exceeds the maximum level of the past. Additionally, a firm can deduct certain assets (equipment including

DNA sequencer) used for biotechnology research. As of spring, 1987, there were 27 such deductible items-in biotechnology. The number is expected to increase dramatically in the future.

Commercial Products

Biotechnology, particularly the commercial application of solvent enzymes, is opening new opportunities for Japan's giant consumer electronics firms.

Bio-Washing Machines

Hitachi introduced "Shizuka Gozen For Bio," a fully automated washing machine. Hitachi hopes to compete with Sharp's introduction of "BioWash ESV458," which has been selling 20 percent better than projected demand of 10,000 units per month. Hitachi, the number two washing machine maker, enters the market at the beginning of a "bio boom" in home electronics. Both Sharp and Hitachi have developed fully automatic compact washers designed to use enzyme-based bio-detergents.

Home electronics makers are working in cooperation with enzyme producers to conquer the bio-appliance market. Sharp consulted with Lion in the development of "BioWash," and a Lion executive was present to answer questions when the new machine was presented to reporters. Hitachi has worked closely with Kao Laboratories in the development of its washer, and inquiries to world-leading enzyme

maker Novo Co.'s Japanese subsidiary - Novo Industri Japan - have been on the rise.

Detergent makers have made a conscious effort to offer products effective with these new washers. Lion has added a "sensor enzyme" to its detergent "Dash," while Kao has increased by 25 percent the biotechnology active ingredient in its "Attack" brand

Bio-Dishwashers

The five home electronics giants have also entered an intense cooperative campaign to make dishwashers a household item in Japan. The machines, compact and fully automated, will make use of enzymes to break down rice residue and resistance from housewives.

It is unusual to see cooperation among the big five, but a limited market and brutal price cutting had reached a critical level, and they decided to work together in expanding (through biotechnology) the possibilities of this last "virgin appliance." Currently, only one percent of Japanese households own a dishwasher (50% in the US), providing great prospects for expansion.[28]

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[28] Ibid.

C.9. ENVIRONMENTAL PURIFICATION

Cultivation of bacteria that break down environmental waste as well as bioreactor-induced water treatments through methane fermentation are the major prospects for bio R&D related to environmental purification. Biodegradable plastic, the subject of a development survey included in MITI's 1989 budget, is once again at the center of attention. The Department of Fisheries, too, in its 1989 budget renewed calls for "Testing of Applied Bioplastic Technology Development." Biodegradable nets and fishhooks, one potential response to world outrage over Japan's fishing practices, are under development.

Although biotechnology applications in environmental purification are still in their initial stages, they promise to revolutionize waste treatment and management in Japan's limited environment. According to a BIDEC survey, biotechnology's economic impact in the year 2000 should amount to Y479 billion for water treatment, Y42 billion for sewage treatment (underground), and Y47.1 billion for waste disposal.[29]

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[29] Ibid.

ENVIRONMENTAL BIOTECHNOLOGY: COMMERCIAL PROSPECTS

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FINAL REPORT
September 28, 1990

Environmental Biotechnology: Commercial Prospects

Biotechnology in a Global Economy

BIOREMEDIATION

> ... for all naturally occurring organic substances, there appears to be at least one type of living thing that can eat it... Perhaps, in time, a creature with an appetite for DDT, toxaphene, or teflon will evolve... So here, then, is a challenge for microbiologists. Given that we have already made a mess of our surroundings, what can we now do to clean them up? (1)

INTRODUCTION

Today cost estimates for the cleanup of contaminated soils and groundwater, plus the routine disposal of industrial and municipal wastes, ranges up to $23 billion for the U.S. and $60 billion for the Western European countries (2,3). The price tag for remediation of past environmental pollution and the construction and maintenance of treatment systems for continually-produced waste is unknown for the entire world. But it is certain that the public and governmental demand for a cleaner environment has made it critical to find a permanent, less costly solution. It is this search for a safe, effective, and inexpensive approach to waste treatment which is escalating current demand for bioremediation.

The biological treatment market has changed dramatically since OTA's 1984 report (4). Just a few short years ago, environmental biotechnology was primarily considered a waste water management tool (5). Today, the documented use of micro-organisms to successfully degrade hazardous and industrial wastes found in soils and groundwater has markedly increased the potential applications of this recently rediscovered methodology.

Many scientists and industry decision makers agree that biology-based waste treatment and reduction hold the promise of permanent environmental restoration for some

pollutants without exorbinate expense. A. Keith Kaufman, Vice President/Director of Bioremedial Service Division, Thorne Environmental, Anaheim, California and the President of the **Applied BioTreatment Association**, has recently observed that in the not too distant past biotreatment companies had to scramble to have biology based technologies included in decision documents for site cleanups. " Now, responsible parties and their consultants are actively recruiting bioremediation firms for proposals (6)." Even the national environmental groups have commented positively about the use naturally occurring micro-organisms for waste cleanup (7).

Moreover, [i]t seems that under William Reilly, a new wind is blowing at the EPA, a willingness to investigate biological methods that provide a permanent solution to the problem of hazardous waste disposal (8). Last winter, William Reilly, Administrator of USEPA, emphasized to a crowd of 4,500 at the Hazardous Materials Control Research Institute's annual Superfund conference,

> [t]he enormous potential of [biotechnology when] applied to cleaning up this country and helping us solve some fundamentally important problems, problems that are daunting in their costs particularly.... If a magic torch to fight the twelve hundred headed hydra is to emerge from anywhere, I would expect it to come from our biotechnology research (9).

During his Senate confirmation hearings, Don Clay, Assistant Administrator for the USEPA Office of Solid Waste and Emergency Response, made it clear that he also considered the future of hazardous waste cleanup to be biology-based treatments (10).

Even State officials are speaking positively about bioremediation. Gary Pulford, Director of the State of Minnesota's Superfund program, thinks enough about bioremediation to require the responsible parties to include bioremediation as one of the

treatment alternatives when preparing the ROD for all cleanups. The State of New York's environmental restoration program is circulating a draft bioremediation contractor guidance. When finalized, it will speed up the screening of environmental biotechnology service companies (11).

Yet, this enthusiasm for bioremediation is confined to the application of naturally occurring organisms to our environment. Because today's biotreatment industry relies on pre-selected, but not genetically engineered microorganisms, the educational and marketing efforts made by the firms have addressed only naturally occurring organisms. This has been an intentional focus away from bioengineering by the U.S. industry. For example, when deciding on the name for their recently formed trade association, the companies chose the word biotreatment, instead of environmental biotechnology, in order to avoid negative public reaction and to convey that genetic engineering is not a prerequisite for a microorganism to degrade a pollutant(12).

Fear of excessive regulation, fired by the complicated draft TSCA rule published by EPA in 1989, convinced the biotreatment industry that any suggestion of genetic manipulation of micro-organisms would spell disaster to their low profit margin businesses (13).

> ... [c]ompanies shudder at the prospect of regulations for natural microbes, as do organic farmers and anyone interested in bioremediation. The use of these non-engineered microbes, made by nature, would virtually dry up if the often prohibitive costs of regulatory approval were added to their cost of development (14).

Only three U.S. companies (Celgene, Envirogen, and General Electric), less than 2% of the industry, discuss bio-engineered organisms with the press and their potential customers (15,

16, 17). These firms are addressing the more recalcitrant pollutants, such as methylene chloride, tricholoroethylene (TCEs) and polychlorinated biphenyls (PCBs). This is in sharp contrast to the university research laboratories where interest in the genetics of biodegradation is increasing. While less than a dozen universities were recognized three years ago as having a critical mass of researchers dedicated to environmental biotechnology, pockets of investigators are now appearing throughout the country. The recent USEPA emphasis on bioremediation, and the expectation of more research funds, because of it is expected to recruit even more researchers into the field.

Biotechnology techniques, many developed in medical and agricultural research, are being used to insert enzyme production genes into soil microorganisms, outfitting the organism with information necessary to degrade more difficult pollutants. Microbiologists are characterizing and collecting populations of organisms suitable for environmental restoration. Engineering and agricultural research is analyzing the contaminated media for bioavailability of the target compounds. University toxicologists and ecologists are defining the impacts of biologically produced toxic waste byproducts and the potential for naturally occurring micro-organisms to clean up polluted waters and soils without man's intervention. In spite of limited federal research dollars, basic environmental biotechnology principles necessary to the successful, reproducible applications of biological treatment are being discovered in the university laboratories. Albeit, the work is slow without adequate monies.

In contrast to the current unthreatening use of naturally occurring organisms, the deliberate release of bio-engineered organisms for environmental applications still elicites demands for extreme caution by citizens and regulators (18). " [The] ability to add

organisms to the environment never before seen on Earth- unique genotypes that Mother Nature wouldn't recognize- is the wild card that biotech adds to the risk debate (19)." To address the inevitable public questions, an educational process on the advantages and disadvantages to the use of genetically engineered organisms for environmental restoration has to initiated and an understandable regulatory program must be promulgated.

Objectives of this Chapter Segment

This segment will describe the U.S. bioremediation industry as it is organized today; describe how the environmental programs have created a market for biological treatment, comparing and contrasting the U.S. with other countries; highlight current commercial uses of micro-organisms to degrade waste; and close with a short discussion on the future of environmental biotechnology.

Today's U.S. Biotreatment Industry

The first company to produce microbes for waste treatment opened its Roanoke, Virginia doors in 1951. That company is still in business. In the 1950's and 60's, the U.S. biotreatment market expanded to a handful of companies, specializing in the production of microbial cocktails for municipal sewage treatment plants and odor control. In the late sixties, at a time when being one with nature was a social goal, a unique application for microbes occurred which can be given credit for publicizing broader uses for biology-based processes (20).

> In 1968, 800,000 gallons of oily bilge water (20% oil) contained in the Queen Mary ocean liner's tanks was purified by bioaugmentation. Within six weeks

the treated bilge water was clean enough to be discharged into the [Long Beach, CA] harbor (21).

In 1970, the establishment of the U.S. Environmental Protection Agency in 1970 and the creation of environmental statutes governing the treatment of wastes throughout that decade, guaranteed a market for the environmental services industry, to which bioremediation firms belong.

Today, the U.S. biotreatment industry includes over 134 firms, up from 29 in 1985 (22) and has evolved into four segments:

Product. Less than a dozen U.S. companies *manufacture* organisms which are sold as biological treatment products. Most of these products consist of pre-selected or a mixture of naturally occurring microorganisms advertised as additives to improve performance. Product use includes degreasing pipes, degrading food processing plant wastes, odor control, and remediating oil spills.

This small product contingency is undergoing some changes with new firms, such as Environmental Dynamics, Frederickburg, VA, being created and mature firms, such as Flow Laboratories, formerly in McLean, VA, discontinuing their environmental applications product line. Consolidation is also occurring. Environmental Remediation, Inc of Baton Rouge, Louisiana, has recently bought out Reliance Biochemicals, Houston, Texas to expand the companies' production capabilities. The U.S. microbial additives industry is considerably larger than this small production contingency suggests. In addition to the primary producers, many U.S. companies blend and market under their own label combinations of microorganisms from the producers.

The microbial cocktail, the commercial name for individual micro-organisms or

consortia of microbes packaged for sale, is a product line available from Japanese and European companies, as well as those headquartered in the States. Information about individual contracts for the production of environmental microbial cocktails is propriety, but common knowledge within the industry points to a complex web of agreements among U.S. and European firms addressing the production and distribution of naturally occurring, pre-conditioned micro-organisms for waste treatment.

Although there is a limited number of U.S. firms offering batch reactor services for the production of environmental microbial additives, according to one industry source the existing U.S. facilities have adequate production capacity to meet increased demand (23). However, the confidence in existing capability is not universal. The Marine Spill Response Corporation has included in initial scoping papers, the potential construction of fermentation units at strategic locations for rapid production of microbial soups for off-shore or in-the-bay oil spill remediation. Because micro-organisms multiply quite rapidly under controlled conditions, the production on-site of selected organisms can serve to supplement existing commerical capacity. Such small scale production facilities are already appearing in the bioremediation hardware market (24).

The existing production units may be limited for second generation waste degrading microbes. Little U.S. commercial capacity is currently available for the production and packaging of anaerobic micro-organisms and for the production of pure cultures. Moreover, no biotreatment companies at this time sell genetically engineered organisms. Future federal and state regulations may require specific facility design for such product lines.

Firms Specializing Exclusively in Bioremediation Services. The biotreatment boutiques make up the majority of this country's biotreatment industry (at least 60 firms). These firms are small, with the average number of employees below thirty. The majority of these companies were founded by a scientist or engineer convinced that biology-based waste management can be commercially viable. Some of the firms began in university laboratories (such as Southern BioProducts, Atlanta, Georgia) while others were spun off from larger companies (such as Coastal Biotechnology, Inc. Bismarck, N. Dakota). Most of these boutique firms have relied on laboratory analytical services or equipment sales to maintain income as they develop their bioremediation services component. A few have had the backing of venture capitalists so that the firm can focus solely on environmental biotechnology.

These smaller biotreatment companies serve as a pool of expertise for larger full service engineering and consulting firms through subcontracts. However, some of the firms have become disenchanted with the larger environmental services companies and seek to contract directly with the waste generator or responsible party.

Analyzing the site or waste treatment facility for indigenous microbial activity, adequate nutrients, suitable moisture, and appropriate oxygen is one service provided by the smaller firms. Enhancement of indigenous micro-organisms by nutrient addition, batching up pre-conditioned organisms found at the site, utilizing off-the-shelf microbes selected for contaminate activity and designing engineering systems to mix the soils or water with the bio-mass are other mainstays of the boutique bioremediation companies. This segment of the industry is a source, and often the patent-holders, for biotreatment hardware, such as soil

slurry mixers, monitoring equipment, and mobile biological reactors (25).

Multi-disciplinary Environmental Services Companies. In 1988, few of these companies offered inhouse bioremediation expertise. Historically, those firms competing in the waste water market were more likely to employ biological treatment specialists than those focused on the hazardous waste markets. Times have changed. Today engineering and construction firms routinely offer at their trade show displays and in their advertisements bioremediation expertise (26). Some firms, such as Thorne Environmental, Anaheim, California, consolidate with independent biotreatment firms, (in Thorne's case, Biota) to provide its clients with proven expertise; while, others, such as EMCON, Groundwater Technology, OHM, and IT, hire individuals to create a separate inhouse professional group. A third approach followed by EBASCO, Bechtel and Environmental Resources Management is to hire a limited number of bioremediation professionals to recommend which projects are appropriate for biological treatment and to manage subcontracts with the bioremediation speciality firms. This latter group may choose at a later date to expand their inhouse capabilities.

Generators. A significant fourth player in the private sector is the waste generator with biological treatment specialists on staff. According to U.S. E.P.A.'s RCRA Orientation Manual, a generator is any facility owner or operator or person who first creates a hazardous waste (27). Although the expertise located in such user firms may not be available to other buyers of the technology, the presence of these skilled individuals competes directly with the biotreatment firms for remediation contracts. In addition to employing biological treatment staffs, some of the large chemical and energy companies are now supporting inhouse

research capabilities to perfect biodegradation of their specific production facilities' wastes. Such research may result in biology-based treatment methods and products which can be marketed directly by the mother company or licensed to bioremediation venders.

What Are the Advantages of Biology-based Waste Treatment?

Bioremediation offers three advantages over more conventional waste treatment technologies, such as incinerator or chemical fixation (28).

* Permanency. Micro-organisms can convert a selected number of wastes into carbon dioxide, water and cell mass. For these completely biodegradable wastes, no toxic residues remain to manage. For other wastes which are not completely mineralized by biological actions, biodegradation can transform hazardous chemicals into stable more benign, less toxic compounds.

* Less costly. The capital costs of biology-based systems are relatively low compared to other treatment technologies. Even the workhorses (the micro-organisms) of bioremediation self-replicate. In some cases, in situ bioremediation may be utilized without escavation or demolition of buildings. For these reasons, the costs of bioremediation should be lower than those systems with more expensive input requirements (29).

* Public acceptability. Bioremediation offers the public a treatment process which relies on "natural" degradation, transforming hazardous wastes to familiar compounds such as carbon dioxide and water. The biotreatment system design, itself, is non-threatening. For example, some bioremediation systems may only require the removal of contaminated soils and groundwater to a tank which looks like the familiar sewage treatment plant or similar

to a vat used to make beer or wine. Moreover, in situ bioremediation does not even require moving toxic wastes or siting a treatment unit. Such in place treatment minimizes the public and environmental risks created by the handling of waste required for treatment.

Today's bioremediation industry relies on naturally occurring micro-organisms. The press and public interest groups have fostered caution about allowing the deliberate release of any organisms which have been genetically manipulated; but the use of naturally occurring organisms for waste treatment has sparked little public opposition and can be done without even notifying a regulatory agency (30).

What are the Limits of Today's Commercial Environmental Biotechnology

The economic and regulatory barriers to bioremediation have been discussed by other authors (31,32) and are included in Tables 1 and 2. But the removal of these non-scientific barriers will not guarantee maximum utilization of biotreatment. Four distinct scientific problems continue to hinder the broader application of biology to waste treatment and cleanup (33,34).

-> There are no official measures for success- bioremediation performance standards are relatively unvalidated.

-> Successful mineralization of pollutants has been limited to relatively easy-to-degrade compounds. Biology-based degradation of recalcitrant compounds must be improved (35).

-> Waste site dynamics as they impact the success of biodegradation are uncharacterized. It is difficult to predict whether a biology-based treatment will work across different waste

types and environments.

-> Genetic characterization and control of microbial degradation are still in their infancies.

But Does It Work?

> " We have strong evidence that bioremediation works. We have no evidence that these microbes have any harmful side effects. In my judgement, we will shirk our responsibilitiy to current and future generations if we don't pursue bioremediation will all prudent speed." Garry Maur, Commissioner, Texas General Land Office, July 12 Press Release.
>
> " It is generally recognized that, under laboratory conditions, microorganisms can degrade many of the most often encountered environmental contaminants (36)."
>
> " Most Swiss researchers believe that biology-based treatment has scientific merit (37)."

Detailed descriptions of the field applications of environmental biotechnology using naturally occurring organisms have become numerous in the last two years. The design of the treatment systems and examples of successful remediations have been covered by previous OTA publications (38,39), symposia proceedings (40,41), and articles (42). A compendium of commercial applications was published by the Applied BioTreatment Association in 1989 (43). An ongoing NATO/CCMS pilot study on "Demonstration of Remedial Action Technologies for Contaminated Land and Groundwater" and programs managed by the U.S. Environmental Protection Agency's Office of Environmental Engineering and Technology Demonstration are examples of U.S. sponsored work to document under what conditions bioremediation can be used for waste treatment.

To provide the necessary level of confidence to the purchaser of a new technology, to the regulator of the use of that technology, and to the potentially impacted citizen

requires a systematic compilation of information generated by standardized testing procedures and measurement units. The difficulty is that such standardized data has not yet been collected for remedial actions relying on biodegradation.

The U.S. Market

The U.S. waste water treatment, environmental restoration and hazardous waste management markets are large. In 1988 OTA's U.S. Investments in Biotechnology, costs to remediate already polluted land were estimated to be as high as $300 billion over a 50 year period and for waste disposal gross annual costs were projected to be $2.4 billion (1984) with a projected increase to $13 billion by 1995 (44). These estimates did not include the private sector costs for on-site waste treatment to meet the Clean Water Act's pre-treatment standards and for the Underground Storage Tank program.

The bioremediation industry's portion of this lucative market is extremely small at this time. But the market potential is great (45). Much of the hazardous waste contaminating soil and groundwater at abandoned sites, the industrial waste received by municipal water treatment plants (much of which should now be treated onsite by the generator), the petroleum product leaking from underground storage tanks and the process waste generated by U.S. industry can be degraded by micro-organisms.

U.S. EPA's breakdown of waste types covered under this nation's waste management and treatment programs suggest that biological treatment could be used for as high as 65% of the current U.S. remediation market (46,47). According a 1989 report published by the Applied BioTreatment Association, the national trade association for the biotreatment

industry, over forty wastes have been degraded commercially (48). In 1988, OTA identified 16 different waste streams undergoing on-site remediation and 40 pollutants which are known to have been degraded or transformed by micro-organisms (49).

The Japanese and OECD Countries' Bioremediation Market

To forecast the current and future markets for bioremediation in the Japanese and EC countries requires detailed country specific information on the following four elements:

1. the country's environmental regulatory programs
2. the nation's research priorities
3. the size of the biotreatment industrial sector
4. the public's comfort level with pollution in general and with biology-based treatment methodologies in particular.

The existence and enforcement of environmental regulations are prerequisites to the formation of a waste treatment market (50). Chart 2 describes the Japanese and OECD environmental programs.

When asked whether environmental regulations are creating a market for waste treatment in both the Pacific Rim countries and in Western Europe, the inevitable answer is "not to the same degree as is happening in the United States (51)."

In Hong Kong and Japan, the businesses are expected to be responsible for pretreating waste before it is discharged or land disposed. Few enforcement officials can not cover the large number of generators tightly packed in highly populated areas. "... Hong Kong's 'fragrant harbor' is now famous among marine biologists as one of the most polluted

marine environments on our planet (52)." Firms in Hong Kong often house their production facilities in multi-story buildings with different companies on each floor. There is no room for waste treatment on site and no common drainage system exists to pool contaminates at one centralized treatment plant (53). Two of Hong Kong's major industrial pollutants are dyes and heavy metals. Fountain Set, a large fabric dyeing factory, has announced that it will spend $1.9 million U.S. on pollution control equipment when it builds its new factory. Since the private sector must fund waste treatment in these two countries, cost, not regulations, appears to play a major market role.

Similar to the U.S.'s Clean Act's financing of the POTW construction in the '70s, public monies have become available in Taiwan for environmental problems- $10 billion has been set aside to finance the creation of a waste management infrastructure. At least a portion of that funding ($1.1 billion) will be used to build and operate waste water treatment facilities (53). Today in Taiwan, pollution control is recognized as a business. A recent ChinaTrade article titled MARKET OPPORTUNITIES: Structure of Taiwan's Environmental Protection Market illustrates this. Chart 3 provides a historical view of the Taiwan environmental budget (54).

On the other side of the globe, " ...[d]espite significant developments in waste treatment processes throughout the OECD, their adoption by industry has been described as problematic in many countries reviewed, because of lax regulations which encourage the payment of fines by industry for waste emission rather than the utilisation of efficient industrial treatment systems (55)." One U.K. observer commented that "it is often cheaper to dig the waste up and carry it off to a landfill than to treat it (56)." As noted in Chart 2,

the U.K. allows co-disposal of hazardous waste with domestic garbage so the cost of management for both types of wastes must be the same. " In Switzerland, punitive financial penalties for the discharge of industrial wastewater do not exist as a means for coercing industry to comply with stipulated discharge standards (57)."

In contrast to the Asian vision of potential profit to be gleamed from promoting environmental responsibility (58), Dr. G. Hamer of the Swiss Federal Institute for Water Resources and Water Pollution Control and the Swiss Institute of Technology has written that "[p]ollution control costs industry money and makes industry, in its own view, less competitive in world markets. In fact, until only a few years, much of industry regarded investment in and operation of ...effluent treatment facilities as money done the drain... (59)."

Perhaps reflecting Dr. Hamer's observations and to provide equal access to waste treatment for all industrial sectors, the Netherlands, Belgium, Denmark, and Germany have centrallized waste treatment facilities. Those handling recurrent solid hazardous waste do not appear to utilize biological treatment at this time; however, these countries have well maintained waste water treatment systems which rely on micro-organisms. The primary bioremediation focus in these countries is the use of biostimulation to encourage indigenous organisms to degrade wastes in contaminated soils and groundwater (60). In contrast to publically run treatment and disposal facilities found in northern Europe, Italy prefers private sector waste management and cleanup services (61). The Italian tourist industry has created a market for environmental restoration. Work is underway at a popular beach to disperse algal mats biologically. France has diversified privately run waste management and

remediation services, with French firms dominating the private sector market.

Although stronger enforcement could generate more demand for waste treatment, public expectations in both the Pacific Rim countries and in the European Community are forcing the governments to inventory contamination problems, to actively participate in cleaning up existing pollution, and to monitor the effectiveness of waste treatment for newly created wastes. Dr.-Ing.Gerhard Sierig of Berliner Stadtreinigungsbetriebe, "A high standard of living coincides with the quantity of the environment-in the air, soil and water. It can only be preserved when the amount of waste is reduced by new technology and when waste disposal technology is improved further." (62)

The United States, in contrast, has an elaborate environmental protection program already in place. Moreover, unlike many other countries, the enforcement of that program is generating a market for environmental cleanup. Cleanup goals and the size of the problem, the universe of waste management facilities, leaking underground storage tanks, and abandoned sites with contaminated soils and ground water, are better defined for this country than for others surveyed. The environmental pollution program is one of this nation's top priorities (63).

Priorities for Environmental Biotechnology Research

National priorities can provide an excellent window into the future of biology-based treatment methodologies. Given that public demand for environmental restoration and for more permanant, less expensive waste treatment methodologies will continue to increase in the near future, then a brief look at selected research and technology transfer programs may

serve as a bioremediation indicator.

Of the nations covered in this Chapter, Canada merits special attention for its no nonsense approach to commercialization. The Canadian government has chosen the development of a biotechnology industry as a national priority. Three areas of government emphasis in the environmental biotechnology field have been identified: (1) heavy metal removal from sludges; (2) dewatering of sludges, and (3) biosensors for the computer control of waste water treatment plants (64). As discussed in a later part of this chapter, the Canadians continue to improve bioleaching technologies and the applications of micro-organisms to mining and oil recovery. Knowledge gained in these fields is directly applicable to heavy metal removal.

Japanese research is jointly done by industry and the government. Water pollution appears to be a high priority for improvement. "Waste water treatment and utilisation represents another massive government programme sponsored by [the Japanese Ministry for International Trade and Industry or] MITI, the funding of which rose dramatically from Y 20 million in '85 to Y 1072 million in 1986. MITI's concentrated efforts to develop a waste water purification process based on biotechnology reflect a keen expectation amongst experts worldwide that waste treatment will represent one of the areas most profoundly affected by biotechnology developments." (65) Contrast this emphasis on water pollution with an observation made by Hugh Russell at USEPA's Ada Oklahoma Groundwater Research station. Dr. Russell could not remember a Japanese observer visiting the laboratory, although many Europeans routinely come to Oklahoma for discussion on groundwater bioremediation (66).

The Federal Republic of Germany's Gesellschaft fur Biotechnologische Forshung mbH or GBF's program on Biological Decontamination of Environmental Pollutants was initiated in 1987. This multi-disciplinary program, common in the environmental biotechnology research field, focuses on the the utilitization of natural microorganisms to degrade toxic chemicals. But work on genetically engineered micro-organisms (GEMs) is planned. In consultation with other nations' researchers, including those at USEPA's Gulf Breezes laboratory and at the University of Tennessee's Center for Environmental Biotechnology, the GBF's Dr. K. Timmis and his associates are working on the elucidation of metabolic pathways involved in contamination degradation. Once these pathways are understood, construction of GEMs with specific degradation properties will be explored (67).

Dr. Neil Hurford, head of the Biological Treatment Division at the United Kingdom's Warren Spring's Laboratory, highlighted three environmental biotechnology focus areas: composing of municipal wastes, removal of metal contaminants, and management of volatile organic emissions. The U.K.'s interest in biological systems stems from their relative simplicity and low cost (68).

Contrast these representative international programs with the more diffuse U.S. focus on bioremediation. The first observation is that the U.S. Congress and the Administration have not established national priorities for environmental biotechnology, in contrast to the Canadians, Germans, and Japanese. Although U.S. EPA, the Defense and Energy Departments are supporting many projects related to bioremediation, the direction of those projects involves many individuals and up to date knowledge about all the bioremediation

work done in federal laboratories is difficult to obtain (69).

In 1988, an international group of distinguished scientists met in Gatlinburg, Tennessee to set a national basic research agenda for environmental biotechnology of hazardous waste. The purpose of this workshop was "to define limitations in the current knowledge base and to develop a research agenda and strategy that will lead to the successful practice of environmental biotechnology (70)." After two years, although some of the research identified by that report is underway at U.S. and a limited number of foreign universities, there is still no national directive for answering basic environmental biotechnology scientific and engineering questions.

Similar to other countries, the majority of the U.S. bioremediation research funding is spent on applied research topics. One country to watch is Taiwan, which plans to increase its environmental protection investments from 3.41% to 8.73% of its GNP, and have emphasized increasing R&D on techniques to detect environmental quality (bioindicators) and on control of secondary pollution from waste disposal (71).

Barriers to the Application of The Technology

At this juncture, the successful application of environmental biotechnology to waste treatment depends on the skills of the vender more than on the capabilities of the microorganisms. An organism with appropriate genetic information to degrade specific or classes of toxic wastes must be kept alive to be productive. In the near term, the expansion of bioremediation will depend on increased in the field use. Analysis of the conditions which have been proven to influence rate and effectiveness should be made and shared.

The required field experience with naturally occurring microorganisms is accumulating both in the United States and in Western Europe. Less than half a dozen bioremediation projects have been done in the U.K. (71). But the eminent use of bioengineered micro-organisms for enviromental cleanup is not likely. With the exception of Italy, the EC is awaiting the approval of the environmental release directives by individual members. And in Japan public opinion is not encouraging the use of genetically engineered organisms for bioremediation according to a Newton, a popular Japanese science magazine, survey. According to Douglas McCormick, editor of BioTechnology, the pool's results reflect the opinions of a scientifically sophisticated audience and are for that reason much more troubling. Seventy eight percent of those surveyed were apprehensive to learn that a deliberate release of genetically engineered microbes might occur in the United States and ninety percent rejected the premise that releases can be environmentally safe (72)."

The use of bioreactors provide more control of the environment inwhich the organisms must work and is already generating a steady stream of data upon which one can judge success. The recent Clean Water Act pre-treatment regulations and concern in Europe about industrial waste water interferring with the treatment of municipal waste waters will provide incentives for the continued development of industry specific on-site bioreactors. Both Japan and Canada are emphasizing the development of biosensors to monitor biodegradation and of the equipment to continually adjust reactor conditions so that optimum biological activity is maintained.

As discussed earlier, predictability is a major barrier to the use of biological treatment systems. The trend in commercial demand for bioremediation is for in situ applications.

Such applications are the most difficult to control and methods to predict success are only now under study at the universities.

In the spring of 1990, President George Bush witnessed the biodegradation of napthalene by a bioengineered organism. The microorganism's emission of bioluminescence in parallel with the production of a naphalene degradation enzyme provided a tool which can be used to predict effectiveness. The applications of this recombinant organism as a biosensor to characterize the microbial population and its degradative capabilities for waste water treatment and contaminated groundwater systems is important to the growth of this field (73,74).

For in situ soil and groundwater remediation projects, field work must be monitored to demonstrate that microbial action is the cause of the disappearance of the target pollutants, not just evaporation (75). Consistent data must be gathered (Chart 3). Treatability studies must be standardized. Descriptions of the cleanup sites must use the same parameters. " The difficulty in determining the efficiency of achievement of technologies as a result of the absence of standardized test protocols," was identified by the New York State Center for Hazardous Waste Management as a major impediment to the implementation of alternative treatment technologies (76).

These barriers exist whether the organism used for bioremediation is genetically engineered or naturally occurring. An acceptance by the scientific and regulatory communities that biology-based waste treatments relying on naturally occurring microbes do consistently degrade the easier compounds, such as petroleum wastes and cresote, is critical before genetically engineered microorganisms are used in the field to degrade the more

recalcitrant pollutants.

Will Bio-Engineering Play a Part in Environmental Applications?

Yes... The first role will be to serve as indicators for bioavailability of pollutants, toxicity of byproducts, and mineralization capabilities of microorganisms.

But the field application of genetically engineered microorganisms will occur within the next three years. The first out-of-the-laboratory work will be done in bioreactors because conditions for microbial survival and monitoring of breakdown products are easier to control in a closed system than in an open field.

The potential savings from the use of biology-based treatments compared to conventional incineration and the interest of generators to limit their long term liability for wastes are positive reasons for the second generation of environmental biotechnology to leave the university and federal laboratories for field applications. In the United States and the European Community, the growing confidence of the government, private, and academic institutions that environmental biotechnology offers a more ecologically sound approach to waste remediation may play the most important role in moving the GEMs to the field.

BIOLEACHING and MINING

A new term has been coined for this field: biohydrometallury. Since OTA's 1984 review of environmental applications, the international focus has expanded. Research has found that optimization of microbial action for bioleaching and concentration of minerals follows some of the same principles being observed for bioremediation and that bioleaching

and mineral concentration may have applications in the waste cleanup area.

The United Kingdom, Canada, South Africa and the United States have ongoing programs in biohydrometallury. The Canadian Center for Mineral and Energy Technology is the lead governmental research agency. One area of focus for the Canadians is uranium bioleaching. 90,000 pounds/month of uranium is now being bioleached from one mine. The biological mitigation of acid mine drainage is another Canadian project. Drainage from a nickel mine has been neutralized from an acid pH of 2.8 to a pH of 6.2 by anaerobic microorganisms (77).

According to the U.K. Warren Springs Laboratory, large pilot plants have already demonstrated improvement in efficiencies and economics of gold recovery by utilizing biological pretreatment with conventional cyanidation and gold recovery. The Laboratory offers bacteria which will use reduced forms of iron and sulfur for growth and operate over a wide range of temperatures. Difficult to extract gold deposits in sulphidic matrices are the target for this process (78).

A paper presented at the 1989 International Biohydrometallurgy Symposium Proceedings summarized the requirements necessary for the genetic engineering of T. ferrooxidans, the workhorse of bioleaching, and a discussion of the state of the art by Dr. Douglas E. Rawlings, University of Cape Town, South Africa. The talk suggested that the rate of pyrite oxidation by naturally occurring microorganisms "may be too slow to permit the economically competitive leaching of certain ores or concentrates (79)."

More sophisticated methods for detecting indigenous organisms and improving their action on petroleum have cooled researchers and industry, in the near future, on the need for genetically engineered organisms. Microorganisms have been found in deep subsurface locations (80) and scientists now agree that petroleum deposits are not sterile but offer microorganisms already conditioned for most deposits unique ecosystems. Moreover, many oil deposits are surrounded by geological formations which are easily plugged by microorganisms, making broad scale injection of any non-indigenous microbe difficult. One organism (called an ultra-micro) has been patented that is small enough to penetrate some of the deposits and the University of Oklahoma has patented a biosulfactant producer.

According to Michael J. McInerney at the University of Oklahoma 327 billion barrels of U.S. oil cannot be recovered by conventional technology, but may be accessible through enhanced oil production. This volume is 2.5 times as large as the amount of oil produced by the United States since 1983. The actual enhanced oil recovery production has been low, with no greater that 5% of the total U.S. production even though a variety of DOE incentives have been available. Other countries, such as Canada, have projected that one third of its oil recovery by the year 2010 will utilize enhanced oil recovery techniques (81). It is possible that the latest middle Eastern crisis will drive the demand for this approach, but the recent advent of horizontal drilling may satisfy the oil companies's need for more yield in the short term.

Although most of the major oil companies have inhouse staff investigating and perfecting MOER, Dr. McInerney predicts that the methodology's low cost may appeal more

to small field operators who have already pumped and sold the easy to get component of their field. (82)

Microbial enhanced oil recovery suffers from lack of predictability. Just like the use of micro-organisms for hazardous waste remediation, the use of microorganisms for oil recovery is site specific. Individual oil deposits have unique characteristics which impact the ability of microorganisms to mobilize and displace oil. " An understanding of the microbial ecology of petroleum reservoirs is a prerequisite to the development of any EOR process whether it is a microbial process or not, since an inappropriate design may accelerate the detrimental activities of microorganisms, [such as corrosion, reservoir souring, and microbial degradation of crude oil] (83)." In other words, the basic environmental biotechnology research underway for contaminated soil and groundwater will provide much needed information to those working on MEOR.

SUMMARY OF ENVIRONMENTAL REGULATORY PROGRAMS

Those Creating a Market

Belgium The Ministry of the Environment delegates environmental protection to the country's three regions. The Flemish Public Waste Agency (OVAM), one of the three regional authorities, was created in 1981 with the authority to plan, regulate, and establish waste management facilities. The Agency also supports some research and development of waste processes.

Canada Environment Canada has the role of gathering and disseminating information, developing national guidelines, and conducting research, development, and demonstration activities plus the direct responsibility of remediating federal lands. The Provinces implement the "Waste Site Disposal Program." This program has three major phases: (1) identification and ranking for cleanup of all operational and closed waste disposal sites; (2) preliminary field assessments of all sites, and (3) detailed field assessments. Limited ground water contamination has also been gathered. According to EPA, the majority of the Canadian hazardous waste sites are already being addressed.

Denmark Laws are in place which provide for a packaging/transport system, a transfer station system, and a central treatment plant (Kommunekemi) for hazardous waste. Local governments are responsible for permitting and the establishment of a collection system. In 1985, approximately one fo:th of the hazardous waste was treated at the point of generation.

Federal Republic of Germany The Waste Disposal Act of the FRG passed in 1972. Requirements include cradle to grave tracking and management of hazardous waste and special regulations to protect against water pollution. State governments are responsible for the implementation. The generator has to pay the full cost for waste disposal.

Seventeen incinerator facilities and 23 physical/chemical treatment plants are available in West Germany. Highly chlorinated materials (but not PCBs) are incinerated at sea. A salt mine in Kassel, receives 45,000 tons per year. In 1982, Germany produced 4.5 million tons of special wastes and imported 40,000 tons. The majority of the 180,000 tons exported from FRG went to GDR.

Landfill capacity is small for hazardous waste. The German State Ministers for Environmental Affairs has directed each State to provide sufficient capacity for its own disposal needs.

France An organic act for environmental protection was passed in 1975 and has been amended several times. The law ended unauthorized dumping, directed the construction of treatment centers and the promulgation of regulations. Treatment of used oil is included. The National Agency for Waste Recovery and Disposal (ANRED) promotes new technologies, serves as a national waste treatment information center, and provides financing for projects in which a national economic interest is present. For water pollution related activities, the French Basin authorities are responsible for management and control.

Waste transportation, collection, disposal and recycling are all done by the private sector. The waste treatment industry is highly diversified, with both small, specialized facilities (chromium, cadmium, mercury) and ten centers for treating oil and solvents. Incinerator capacity has been saturated and existing hazardous waste landfills are reaching their capacity.

Japan The Japanese Waste Disposal and Public Cleansing Law was passed in 1970. The law provides that enterprises must treat their industrial wastes themselves. Regional disposal facilities are under consideration with emphasis on waste water treatment. The local prefectures are charged with antipollution control. However, too few inspectors are available to cover all generators. Hazardous waste are to be pretreated or solidified in concrete before being deposited in landfills. No PCB treatment is currently available. Roughly 85-90% of final disposal is landfill, with the rest subject to ocean dumping.

Netherlands In 1983, the Interim Soil Cleanup Act was enacted. This law surveyed sites with soil contamination which require remediation. The sites are remediated by the polluter unless he can not be located, then the federal government splits the cost with the local authorities 90:10. 1,600 sites have been identified.

The Chemical Waste Act of 1979 addresses tracking of waste disposal. Enforcement could be improved however.

United Kingdom The U.K. has a uniquely strong emphasis on government control of land use. In January, 1990, a parliamentary report was released on contamination of land available for development. The House of Commons' response directed the establishment of local registers of potentially contaminated land (31).

Co-disposal of hazardous waste is the technology of choice in the U.K. The presence of domestic solid waste assists in the attenuation of the hazardous waste according to proponents of this approach.

The Control of Pollution Act of 1974 delineates the federal and local authorities' responsibilities. The major role of the Department of the Environment is to develop guidance documents for the handling and disposal of hazardous waste. The Department of the Environment's technical support is provided by the Harwell Laboratories, which solely addresses the development of waste management technologies.

Water pollution discharge licenses are based on the premise that "hazardous substance releases to the environment must be limited to the amount which will not exceed the capacity of the receptor to absorb the substance with the occurrence of harmful effects." Water permits are issued by the Regional Water Authority.

The reliance on local authorities for all aspects of hazardous waste management results in a lack of enforcement and standards uniformity.

Switzerland Water quality criteria were decreed in an ordinance issued in 1975 and effective a year later. Fifty-two parameters are used to describe these water quality criteria. Ninety percent of the domestic waste water is treated by conventional mechanical-biological technology. Eighty five percent of the industrial waste waters are discharged to public sewers and treated at Swiss POTWs.

Primary REFERENCE FOR THIS CHART: Bio Technology and the Changing Role of Government

TABLE 1

Economic Barriers to the Commercialization of Bioremediation

* Venture capital has been slow to invest in the technology.

* Today's bioremediation relies on trade secrets, not patent protection. Currently, the biological treatment machines are naturally occurring organisms which can not be patented and can be reproduced by one's competitors. This lack of propriety property subjects the industry to constant competitor stress.

* The majority of the bioremediation firms are small and lack sufficient capital to finance sophisticated research and product development programs. This is a problem for utilizing naturally occurring organisms, but a crisis for the development of bio-engineered products and related services.

* Bioremediation lacks a strong publically funded research base. Federal research dollars have been scarce to support the discovery or improvements of biology-based treatment.

* Marketing has been historically done by individual companies, few firms exist which act as brokers for the technology. Such an arrangement is manpower intensive.

* Experienced manpower is in short supply. Universities are only now establishing curriculum for bioremediation specialists and continuing education programs are not common. With the limited experience available, companies must compete for additional professional staff, potentially driving the cost upward.

* The key marketing promise of the biotreatment industry is less cost for remediation. No academic or regulatory agency has published a study analyzing the costs of biological treatment compared with other technologies, such as incineration. The only information currently available is found in individual companies marketing materials.

TABLE 2

Regulatory Barriers for the Commercialization of Bioremediation

* Regulatory coverage still unclear. No definitive statement has been made by U.S. EPA that the use of naturally occurring micro-organisms for environmental cleanup will be exempted from TSCA requirements. However, it is certain that genetically engineered organisms will face a lengthy regulatory process until USEPA gains sufficient experience in environmental applications necessary for speedy reviews.

* One OSW rule inadvertently favors existing waste technologies. The residue concentration for land disposal of treated wastes is set by the Best Demonstrated Available Technology (BDAT). Some of these targets which are based on detection levels or incinerator performance, not on risk. In the field, biological treatment may be able to reach the higher residue concentration (based on risk), but not the lower (based on technology).

* LDRs limit reactor design. The recent land disposal regulations promulgated by the Office of Solid Waste prohibits the recirculation of contaminated groundwater through an in situ bioreactor arrangement, a common design for bioremediation of contaminated soils and groundwater.

* As the federal hazardous waste universe expands, bioremediation companies will become have one more regulatory agency which to work. The listing of petroleum sludges and creosote as hazardous wastes will bring a large ongoing bioremediation market under the federal program, in addition to state programs.

* How to demonstrate successful biodegradation is still under development. Treatability studies which are used by the regulatory agencies to determine the efficacy of a waste treatment regime have not been standardized for biological treatment.

* In the past, bioremediation may have been rejected because of an inadequate understanding of potential applications. The knowledge about which waste and characterization of the contaminated sites is still evolving. For example, EPA training materials printed before 1990 flatly stated taht biological treatment is not appropriate for dilute solutions or for heavy metals. At the state time that these guidances were being circulated to federal and state regulators, the Interior Department's Bureau of Mines was initiating a program to explore the application of bioleaching and bioconcentration to sites contaminated with heavy metals.

Venture Capital Notes

Four venture capital companies, at least, appear to be seriously watching bioremediation. I can only identify Domain Associates, out of Princeton as having invested in firms. Jim Blair is the contact for Domain. I think that Domain has invested in Ecova and in Biotrol.

The other companies are Hamburgh and Quest in San Francisco (Environmental Technology Fund); First Capital Analysis (Environmental Venture Fund) in Chicago; and Scully Capital Investments in D.C.

Background: Larry J. Scully, President of Scully Capital Services, is seeing bioremediation catching on because of the renewed hope that the firms will be commercially viable and therefore provide a sound return.

Key reasons for the upsurge in interest:
1. Wm Reilly's identifying the biological treatment as the wave of the future
2. the escalating cost of incineration and the hope that bioremediation can be cheaper

Continuing question- does it really work?
What can one company offer that makes it competitive for investors' money- propriety product or service (patents).

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OTA REPORT, INTERNATIONAL BIOTECHNOLOGY PATENTING

March 1990 Draft
Responding to Panel Recommendations

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OVERVIEW

This report focuses on several discrete problems for American competitiveness in the field of biotechnology. In the body of the report itself (page 1 et seq.) there are three specific topics which are considered that may require legislative or treaty action.

In appendicies taken from existing materials that are not generally available, the international framework for patents, the Paris Convention, is considered, as well as some of the problems for Americans that are found in the setting of Japanese patent law.

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INTERNATIONAL BIOTECHNOLOGY PATENTING

American competitiveness in biotechnology focuses largely on securing valuable patent rights for Americans in Japan and Europe, with a particular focus on Japan. The reason that there is a focus on Japan is threefold. First, the self-evident importance of biotechnology to Japan as a priority industry means that if Americans are to have an even chance, Americans must secure patents on a competitive basis in the Japanese market itself, and not by default give up that market to Japanese. Second, the Japanese consuming public is perhaps the biggest single market for pharmacetuicals in the world (outside the United States), and biotechnology products are playing an ever greater role in the Japanese market. Third, there are greater difficulties for Americans filing patents in Japan than in Europe, in part due to the language barrier and in part due to the scarcity of benrishi, the licensed biotechnology registered patent attorneys in Japan who are so few in number yet so vital to obtaining strong protection.

Among the various issues that can be considered in a patent context one may refer to (a) deposit issues, particularly whether the deposits should be freely available; (b) distribution of biotechnology property; (c) specific biotech provisions in the WIPO Harmonization Treaty; and (d) the backlog of biotech patents both Japan and the United States, and the role that this plays in the matter of international patents.

I. POINT (A): DEPOSIT ISSUES

There are three aspects to deposit issues. When Is a Deposit Required? When Should a Deposit be Released to the Public? What is the Scope of the "Research Exemption"?

A. When Is a Deposit Required?

All countries of the world require deposits when it is not possible to reproduce a claimed invention without reference to a deposit. The matter is one for case by case determination on a global basis, and in some cases it can be demonstrated that a patent applicant is able to disclose how to recreate his invention from mere words alone, and then a deposit is not required for purposes of "enablement". In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

Uniquely, however, the United States requires that the "best" sample be disclosed by way of a deposit, if that best sample cannot be recreated from the words of the patent application alone. Thus, in Wands itself, the applicant conceded this point by depositing his best sample to meet the best mode requirement. In Scripps Clinic and Research Foundation v. Genentech, Inc., 707 F.Supp. 1547, 11 USPQ2d 1187 (N.D.Cal. 1989), the patentee hid his best sapmle, and the patent was held invalid. (See the discussion of this case, infra.)

B. When Should a Depcsit be Released to the Public?

A biotechnology patent applicant cannot expect to maintain his magic sample in secrecy forever if he is to be granted a patent, but he should be entitled to an adequate lead time before the rest of the world goes to the American Type Culture Collection (ATCC) and can obtain a sample.

It is axiomatic in every country that if a biotechnology sample is needed to teach the invention, then it must be deposited before the first priority filing date. The issue is one of when must it be released?

The United States permits secrecy up until the grant, often many years from filing.

Japan provides secrecy up until the kokoku, the publication for opposition purposes, so this, too, provides a reasonable period of secrecy.

Germany and the European Patent Office permit access at 18 months from the filing date, which destroys attempts to keep the biotechnology deposit secret for a longer period. Once the door is opened in Europe, then the cat is out of the bag.

C. What is the Scope of the "Research Exemption"?

Once a sample is released from the ATCC that relates to a patented invention, there is a controversy over the degree to which that sample can be used here and in foreign countries.

Japan and Europe today have a statutory "research exemption" that freely permits the use of a patented invention in the laboratory to create new inventions. Thus, an ATCC sample of a monoclonal could be used without patent infringement to create new technology. Whether that new technology could be commercialized without patent infringement would depend upon whether or not the claims of the patent covered the new product.

For example, Japanese law, Article 69(1), in Tanabe & Wegner, Japanese Patent Law, p. 289 (1979), states that: "The effects of the patent right shall not extend to the working of the patent right for the purposes of experimentation or research." European laws and a European view are found in the Appendix, **"LETTER CONCERNING THE RESEARCH EXEMPTION."**

Is it desirable to have a statutory research exemption in the United States patent law? The answer to this question may become clearer if and when the Court gives any guidance by way of dictum when it rules on the appeal from Eli Lilly and Co. v. Medtronic, Inc., 872 F.2d 402, 10 USPQ2d 1304 (Fed. Cir. 1989). The holding in this case deals with statutory construction (whether § 271(e)(1) regulatory testing exemption includes only "drugs" as per the literal wording and the legislative history, or includes medical devices as held by the Federal Circuit below). The Court may very well include guidance on the question of what is comprised by the experimental use exception to patent law.

If a statutory research exemption is desired for American industry, then such a proposal could be, for example:

> **Making or using a patented invention for the purpose of creation of new technology or characterization or comparison of the patented invention for experimentation shall not constitute an act of infringement, provided that this exemption does not extend to commercialization of such new technology.**

II. POINT (B); DISTRIBUTION OF BIOTECHNOLOGY PROPERTY

The distribution of biotechnology property is a contractual matter that is not directly keyed to patents. However, to the extent that any country has a strict policy that a patent applicant must make biotechnology deposits with the American Type Culture Collection (ATCC) or other organization, this opens the door to third parties obtaining biotechnology property. Once the ATCC releases a sample to a third party and that sample finds its way to Taiwan, Singapore or some other country without strong patent controls, the depositor's remedy lies with any contractual violation by the person obtaining the deposit in the first instance. This is hardly a satisfactory result.

III. POINT (C): SPECIFIC PROVISIONS IN THE HARMONIZATION TREATY

A. Biotechnology, the Harmonization Treaty Orphan

In one word, there is nothing in the Harmonization Treaty that deals with biotechnology. Biotechnology experts have been too preoccupied with the Biotechnology Committee of Experts, neglecting the fact that it is in the broader Harmonization Committee that general principles of patent law are established, and which necessarily govern the biotechnology field.

For example, the area of deposits of biotechnology material is governed as to procedures in the Biotechnology Committee of Experts. But, in terms of the substantive requiremnet for deposits, this is governed by the substantive patent law that is under the jurisdiction of the Harmonization Committee.

B. Biotechnology Deposits, A Case Study

At the present time, for example, there is a great debate over whether the United States should maintain its "best mode" requirement for biotechnology inventions. This requirement was new to non-mechanical inventions in the 1952 Patent Act, and recently there have been rather severe holdings of invalidity for failure to meet the deposit requirement. Under U.S. law, only, the applicant is required to "set forth [in the patent specification] the best mode contemplated by the inventor of carrying out his invention." 35 USC § 112.

Prior to 1952, the law was restricted to machines. Thus, the best mode disclosure requirement in R.S. § 4888, as amended, 38

Stat. 958, 959, 46 Stat. 376 was only that "in case of a machine, [the inventor] shall explain the principle thereof, and the best mode in which he has contemplated applying that principle, so as to distinguish it from other inventions * * *".

The "best mode contemplated" required as the final part of the first paragraph of 35 USC § 112 is the subjective best way of carrying out the invention appreciated by the inventor as of the filing date. Compliance with the "enablement" requirement may or may not meet this separate requirement, e.g., where a "mediocre" mode is disclosed in the specification that fully meets the enablement requirement, but which is overshadowed by a better mode that is withheld from the Examiner. Bigham v. Godtfredsen, 857 F.2d 1415, 8 USPQ2d 1266 (Fed. Cir. 1988) ("the 'best mode' requirement refers to concealment of what the applicant believed to be the best mode at the time of filing the application. Questions of adequate written description and enablement are not resolved in terms of the best mode requirement.") See also Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1535, 3 USPQ2d 1737, 1745 (Fed. Cir.), cert. denied, 108 S. Ct. 346 (1987) ("there is no objective standard by which to judge the adequacy of a best mode disclosure, * * * only evidence of 'concealment', whether accidental or intentional, is considered."); DeGeorge v. Bernier, 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985); In re Sherwood, 613 F.2d 809, 816, 204 USPQ 537, 544 (CCPA 1980).

The best example is the Blood Factor VIII:C case, Scripps Clinic and Research Foundation v. Genentech, Inc., 707 F.Supp. 1547, 11 USPQ2d 1187 (N.D.Cal. 1989), oral argument at the Federal Circuit on appeal, January 9, 1990. In this case, patentee Scripps Clinic deposited an enabling monoclonal antibody used in a

chromatographic column to isolate the blood fraction, but failed to disclose its best contemplated monoclonal. The patent was held invalid because although the invention claimed was disclosed fully in the patent, the best monoclonal was not deposited.

As a result, Americans are forced to err on the safe side and deposit with the ATCC (or elsewhere) their best biotechnology samples, samples that would otherwise be kept locked in the inventor's laboratory. Everyone is essentially free to obtain these best samples and freely use them outside the jurisdiction of the United States.

IV. POINT (D): THE BIOTECHNOLOGY BACKLOG EVERYWHERE

A. The Japanese and European Backlogs

The Japanese biotechnology backlog is a serious impediment to small American companies who need the assurance of a Japanese patent for the purpose of exploitation of their invention.

One solution is to greatly strengthen the Patent Cooperation Treaty (PCT) that today permits a preliminary examination of patent applications on a global basis through a PCT application that can be prosecuted in one's home country.

The trouble with the present system is that there is a fixed, non-extendable deadline of 30 months from the priority date to complete the entire PCT phase of examination.

A solution is to extend the PCT phase to 60 months, and then have a complete examination conducted as part of the PCT phase.

If this change in PCT is made, then there should also be international comity as to the results of the examination, with the Japanese and European patnet offices immediately taking the cases filed in their offices up for examination as soon as the PCT phase is complete, and -- in the absence of special circumstances -- pro forma grant them subject to the usual opposition period. Americans, likewise, would have to give a similar effect to Japanse and European cases that come to us via the PCT.

By shifting resources to an extended PCT, this would have the net effect for every PCT filing of this type of reducing by two thirds the examination work of each patent office, as only one of the three major offices would examine a case -- instead of three as today.

By shifting to PCT for the Japanese examination, the American would be able to get a quick examination here at home -- to the extent that the U.S. Patent Office is able to quickly move cases through the pipeline. (This depends to a large degree upon whether the United States is willing to domestically reform its system, as discussed in the following section.)

B. The U.S. Backlog

The U.S. backlog is quite serious in biotechnology, and the solution is rather simple. Most Americans do not need their biotechnology applications examined right away, but since all applications are given equal treatment, those applications that are

"musts" for quick examination are caught in the backlog.

The solution in the United States is selective examination. Under selective examination, applicants could select their cases for priority treatment, and defer the rest until a much later date. Then, everyone would have his cake and be able to eat it, too. The cases of importance would be examined, right away. Those that are not of immediate interest could be put on the Examiner's shelf until a much later date -- and save the applicant some money, too.

To permit such reform, however, public policy demands that the international system of 18 month automatic publication and 20 year term from the filing date be introduced into U.S. law.

As part of § 6.1 of the TRIPs proposal (trade related intellectual property issues) of the Uruguay Round of the General Agreement on Tariff and Trade (GATT), a 20 year patent term from the filing date is already in the works. An overall proposal that has been prepared by an American Intellectual Property Law Association (AIPLA) Committee chaired by Robert Benson ("Benson Committee") specifically includes this proposal.

APPENDIX I: THE PARIS CONVENTION FRAMEWORK FOR PATENTS

(excerpts from Wegner, Comparative Patent Law (1990))

The Paris Convention is the fundamental treaty that secures American rights in foreign countries. Efforts to change the Paris Convention in the past generation have been largely by developing countries seeking to water down this cornerstone of protection for American rights overseas. Clearly, the United States is satisifed with the Paris Convention, as is, and seeks no revision to this "constitution" for international patents. The next Revision Conference of the Paris Convention is tentatively scheduled for Geneva in the latter part of 1991, after the Harmonization Treaty Diplomatic Conference in mid-1991.

Associated with various trade shows on the Continent in the mid-nineteenth century, the Austrians, French and others started discussions leading to what became the 1883 Paris Convention, which the United States ratified finally in 1903, twenty years later, as the 1900 Brussels Revision. Several Diplomatic Conferences have been held since then with mostly minor revisions. The present version is the 1967 Stockholm Revision. Diplomatic Conferences have taken place several times since Stockholm, the U.S. each time snatching inaction from the jaws of defeat (to paraphrase the then Commissioner of Patents and Trademarks in charge of U.S. intellectual property negotiations, Gerald Mossinghoff).

On November 13, 1989, as part of the Seventh Session of the Committee of Experts dealing with patent harmonization matters, it was announced by the Director General of WIPO that a Diplomatic Conference for further revision of the Paris Convention is scheduled for the second half of 1991. The scheduling is tentative, however, as the Governing Bodies meeting in September 1991 must approve such a convention.

I. PARIS, PRIMARY AMONG THE SEVERAL PATENT TREATIES

If there is any conflict between the Paris Convention and other treaties such as the European Patent Convention (EPC) or the Patent Cooperation Treaty (PCT), it is the Paris Convention that governs. Paris came first and binds all parties under the subservient EPC and PCT. Article 19 of the Paris Convention permits such additional treaties, but obviously nothing inconsistent with Paris is permitted.

The EPC and PCT are treaties under Article 19 of the Paris Convention. Article 19 provides that "the countries * * * reserve the right to make separately between themselves special agreements for the protection of industrial property, in so far as these agreements do not contravene the provisions of this Convention."

Every major industrial concern is or can be covered by the Paris Convention rights. For example, if a company is located outside a Paris Convention country, it qualifies for Paris Convention rights if it has a "real and effective * * * commercial [establishment]" in a treaty state. Thus, Article 3 provides that "[n]ationals of countries outside the Union who are domiciled or who have real and effective industrial or commercial establishments in the territory of one of the countries of the Union shall be treated in the same manner as nationals of the countries of the Union."

Every member state must comply with the Paris Convention. But, there is the question whether the local law of a particular country is self-executing or not. The Japanese patent law, for example, has an express provision that gives primacy to the Paris

Convention in the event of a conflict between local and treaty provisions.

In the United States, the domestic implementing legislation that gives Paris Convention rights is 35 USC § 119. Merely because there is a right stated in the Paris Convention does not give that right to an individual in the United States, as the treaty is not self-executing. Kawai v. Metlesics, 480 F.2d 880, 178 USPQ 158 (CCPA 1973).

The U.S. implementing statute (35 USC § 119 "Benefit of earlier filing date in foreign country; right of priority") provides that the priority right is accorded to a U.S. patent application "filed in this country by any person who has, or whose legal representatives or assigns have, previously regularly filed an application for a patent for the same invention in a foreign country" that is a Paris member (or gives equivalent rights).

Two key substantive points of the U.S.-Paris Convention right are spelled out in the first paragraph of 35 USC § 119:

First, subject to filing within 12 months, such filing "shall have the *same effect* as the same application would have if filed in [the United States] on the date on which the application for patent for the same invention was first filed in such foreign country * * *". There is a general view in international circles outside North America that the United States domestic implementing legislation falls short of the Paris Convention because there is no

patent-defeating right given to a foreign patentee as of his priority date, one that is required by Article 4B of the London Revision of the Paris Convention with the modification in 1934 of the ***reserve des droits des tiers***.

Second, the priority right does not give the "same effect" in all respects. In § 119 it is stated that the bar under 35 USC § 102(b) cannot be overcome by Paris priority: "[N]o patent shall be granted on any application * * * for an invention which had been patented or described in a printed publication in any country more than one year before the date of the actual filing of the application in this country, or which had been in public use or on sale in this country more than one year prior to such filing."

II. THE PRINCIPLE OF "NATIONAL TREATMENT"

An American is given a treaty guarantee that he will be treated as well as a German in Germany, as well as a Japanese in Japan and so forth, under the guarantee of "national treatment". Article 2(1) of the Paris Convention sets forth the "national treatment" guarantee:

> Nationals of any country of the Union shall * * * enjoy in all the other countries of the Union the advantages that their respective laws * * * grant * * * to nationals; all without prejudice to the rights specially provided for by this Convention. Consequently, they shall have the same protection as the latter, and the same legal remedy against any infringement of their rights, provided that the conditions and formalities imposed upon nationals are complied with.

Conversely, the American patent system must provide a German or Japanese or other foreign national the same procedural rights in the United States as would be enjoyed by a U.S. national. In this regard, although the U.S. case law denies a violation, there is as clear a violation of Article 2(1) as could be imagined in 35 USC § 104, which denies a foreign inventor a right of priority based upon his acts in a foreign country, where the second sentence of 35 USC § 104 gives certain American citizens special priority rights for inventions made abroad.

Early American statutory provisions had discriminated against foreign inventors under citizenship or residence requirements. Article 2(2) proscribes such discrimination: "[N]o requirement as to domicile or establishment in the country where protection is claimed may be imposed upon nationals of the Union for the enjoyment of any industrial property rights."

There are some narrowly carved exceptions in the treaty where a foreign applicant can receive different treatment. Under Article 2(3), "[t]he provisions of the laws of each of the countries of the Union relating to judicial and administrative procedure and to jurisdiction, and to the designation of an address for service or the appointment of an agent, which may be required by the laws on industrial property are expressly reserved.

Whether the United States law that denies a foreign inventor a right of priority for inventions made in his own country, where even some foreign made inventions of Americans do not face such a bar, this is a key question in the interpretation of Article 2. See § 131.20, Violation of Article 2 of the Paris Convention.

III. THE PRIORITY RIGHT

The applicant in a first-to-file world must gain the earliest filing date possible to establish his rights. Under the Paris Convention, the applicant must win the race to his "home country" (or any other Paris Convention country) patent office, and then have one year to file in other countries with a right of priority based on his first filing.

Certain formal requirements are set forth in Article 4 which are permitted or required. Under Article 4(C)(4) it is stated that:

> No other formalities may be required for the declaration of priority at the time of filing the application [than as set forth in this Article]. Each country of the Union shall determine the consequences of failure to comply with the formalities preserved by this Article, but such consequences shall in no case go beyond the right of priority.

The fundamental positive right given applicants under the Paris Convention is a one year period of priority (six months for designs).

Under Article 4(A)(1), it is provided that "[a]ny person who has duly filed an application for a patent * * * in one of the countries of the Union, or his successor in title, shall enjoy, for the purpose of filing in the other countries, a right of priority during the periods hereinafter fixed."

The period of priority is set in Article 4(C)(1) ("[t]he periods of priority * * * shall be twelve months for patents * * *).

Article 4(C)(4) permits an applicant to reset his priority date by effectively cancelling the first application:

> A subsequent application * * * in the same country * * * shall be considered as the first application [for purposes of starting the priority year] if, at the time of filing the subsequent application, the said previous application has been withdrawn, abandoned, or refused, without having been laid open to public inspection and without leaving any rights outstanding, and if it has not yet served as a basis for claiming a right of priority. The previous application may not thereafter serve as a basis for claiming a right of priority.

The type of application which gives rise to a priority right is a "regular national filing". As stated in Article 4(A)(2):

> Any filing that is equivalent to a regular national filing under the domestic legislation of any country of the Union * * * shall be recognized as giving right to the right of priority.

A definition of a "regular national filing" is given in Article 4(A)(3):

> By a regular national filing is meant any filing that is adequate to establish the date on which the application was filed in the country concerned, whatever may be the subsequent fate of the application.

The leading case on what constitutes a "regular national filing" is an opinion by Chief Judge Markey in Stein Associates, Inc. v. Heat and Control, Inc., 748 F.2d 653, 656-58, 223 USPQ 1277 (Fed. Cir. 1984).

The United States has the most liberal practice in the world in terms of *formal* priority requirements, permitting priority claims late in prosecution or even after grant. Failure to meet the time deadlines may be informally waived (certified copy filed shortly after Issue Fee payment) or cured through reissue. Brenner v. State of Israel, 400 F.2d 789, 158 USPQ 584 (D.C. Cir. 1968); see also Fontijn v. Okamoto, 518 F.2d 610, 186 USPQ 97 (CCPA 1975). The Paris Convention permits a country to limit priority to those cases where there is a claim made upon filing. Article 4(D)(1) provides that to obtain priority a party "shall be required to make declaration indicating the date of such filing and the country in which it was made. Each country shall determine the latest date on which such declaration shall be made."

America liberally permits a certified copy to be filed to perfect the priority claim late in prosecution and perhaps by reissue under dictum in State of Israel. The Paris Convention merely requires that a time limit not be permitted of less than three months in Article 4(C)(3):

> [A copy of the application may be required.] The copy, certified as correct by the [original patent office], shall not require any authentication, and may in any case be filed, without fee, at any time within three months of the filing of the subsequent application. * * * [A] certificate from the same [patent office] showing the date of filing [may be required], and * * * a translation [may be required].

Under Article 4(F) it is provided that:

> No country * * * may refuse a priority * * * on the ground that the applicant claims multiple priorities, even if they originate in different countries * * *. With respect to the elements not included in the [priority] application * * *, the filing of the subsequent application shall give rise to a right of priority under ordinary conditions.

Priority shall be granted where the priority application has a disclosure of the invention that is claimed in the later application.

Verbatim disclosure is not required, but under Article 4H only that the invention claimed in the convention application is one in which "the [priority] application documents as a whole specifically disclose [the claimed] elements."

It seems unfair that an applicant may file a complete disclosure in his "home country" of one aspect of an invention, there is then a publication of that identical aspect of an invention, and then there is a Paris Convention.

As held in In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989), the identical rules for priority under the Paris Convention (35 USC § 119) apply as for priority based upon a domestic (continuation-in-part) application.

No *claim* is required in the priority application. As pointed out in the first portion of Article 4H, "[p]riority may not be refused on the ground that certain elements of the invention for

which priority is claimed do not appear among the claims formulated in the application in the country of origin * * *."

The complete text of Article 4H reads as follows:

> Priority may not be refused on the ground that certain elements of the invention for which priority is claimed do not appear among the claims formulated in the application in the country of origin, provided that the application documents as a whole specifically disclose such elements.

Under Article 4ter, "[t]he inventor shall have the right to be mentioned as such in the patent." The European system goes further and publishes the name of the inventor in the published patent application 18 months from the priority date, instead of only much later when the patent is granted.

IV. THE PATENT DEFEATING "SENIOR RIGHT"

Article 4B guarantees a patent-defeating right to the patentee as to whatever is claimed in his patent, retroactive to his priority date. Any claim in an application of another that has an effective filing date after the priority date is to be denied.

Thus, it is explicitly provided that "another filing [by a third party in the Paris Convention year] cannot give rise to any third-party right * * *." The more complete text of the first sentence of Article 4B states that:

> [A]ny subsequent filing in any of the other countries of the Union before the expiration of the [convention year]

> shall not be invalidated by reason of any acts accomplished in the interval, in particular, another filing, the publication or exploitation of the invention, * * * and such acts cannot give rise to any third-party right or any right of personal possession. Rights acquired by third parties before the date of the first application that serves as the basis for the right of priority are reserved in accordance with the domestic legislation of each country of the Union.

Most countries provide a broader patent-defeating right than required by the treaty. The treaty only requires a "prior claim" approach, i.e., that the Paris Convention patentee is given a patent-defeating right retroactive to the priority date for what is claimed in the patent. The Swiss continue to have this narrow minimum scope definition of the patent-defeating right. Whereas other countries including Germany and Japan formerly had this narrow right as well, today the laws of Japan and most EEC states (including Germany) provide a "whole contents" patent-defeating effect that covers everything disclosed in the priority document that is carried forward into the patent application; furthermore, the patent-defeating effect is created not when the patent issues, but the earlier "laying open" date 18 months from the priority date.

Exceptionally, the United States stands in violation of Article 4B of the Paris Convention to the extent that it does not give a patent-defeating effect for a claimed invention as from the priority date. Defensive priority rights are recognized by the 1934 London Revision of the Paris Convention with the elimination of the reserve des droits des tiers in Article 4B. However, domestic case law has never considered London. See Hilmer I, In re Hilmer, In re Hilmer, 359 F.2d 859, 149 USPQ 480 (CCPA 1966) (no

defensive right as part of priority right under § 119 and hence patent defeating date under § 102(e) is actual filing date, not Paris Convention priority date), and Hilmer II, In re Hilmer, 424 F.2d 1108 (CCPA 1970). See also In re McKellin, 529 F.2d 1324 (CCPA 1976).

V. PRIOR USER RIGHTS (RESERVE DES DROITS DES TIERS)

Reservation of third party rights (*reserve des droits des tiers*) cannot be based upon acts after the priority date. This was an explicit proscription as part of the 1934 London Revision, and is embodied in the first sentence of Article 4B of the present Stockholm text which provides that "acts [in the Paris Convention interval] cannot give rise to any third-party right or any right of personal possession."

The reserve des droits des tiers continues to be a matter for local legislation as to any prior use dating prior to the Paris Convention priority. This is found in the second sentence of Article 4B, providing that "[r]ights acquired by third parties before the date of the first application that serves as the basis for the right of priority are reserved in accordance with the domestic legislation of each country of the Union."

VI. INDEPENDENCE OF PATENTS

The Paris Convention guarantees that certain results cannot be contingent upon what happens to a parallel patent in a second member state in terms of validity (see § 26.10) or the term of the patent (see § 26.20).

VII. INDEPENDENT CONSIDERATION OF VALIDITY

Article $4^{bis}(1)$ provides that "[p]atents applied for the various countries of the Union * * * shall be independent of patents obtained for the same invention in other countries * * *."

Finding that a patent is invalid in one country cannot be used to automatically invalidate a patent in a second country. As stated in Article $4^{bis}(2)$, "patents applied for during the period of priority are independent, * * * as regards the grounds for nullity and forfeiture * * *."

VIII. INDEPENDENCE OF PATENT TERM

Where a patent term is based upon the time from the filing date, the priority year cannot be counted in the patent term. As stated in Article $4^{bis}(5)$, "[p]atents obtained with the benefit of priority shall * * * have a duration equal to that they would have, had they been applied for or granted without the benefit of priority."

As stated in Article $4^{bis}(2)$, "patents applied for during the period of priority are independent * * * as regards their normal duration."

Nineteenth century American public policy found it to be highly objectionable for patents, particularly process patents, to expire in a foreign country before they expired in the United States. Later expiration of a U.S. patent would mean that in the final years of the U.S. patent, the English and other competitors would be free to use the patented process in their home factories,

thanks to the expiration of the parallel patents in those countries. Because of the limitation of American process patents to products made in this country (a shortcoming remedied only a century later in 1988 with the introduction of 35 USC § 271(g)), English and other Europeans could develop a highly competitive market against the patentee in the United States, while the American competitors of the patentee would be shut out.

The public policy that American patents should not extend unduly beyond foreign counterparts is also valid today. Yet, from 1903 forward (when the United States became a member of the Paris Convention), the old law limiting the term of a patent to the expiration date of the earliest-to-expire foreign counterpart was emasuculated. The remnants of this early provision are found as 35 USC § 102(e). See In re Monks, 588 F.2d 308, 200 USPQ 129 (CCPA 1978).

APPENDIX II: THE JAPANESE PATENT SYSTEM, A COMPARATIVE VIEW

(excerpts from Wegner, Comparative Patent Law (1990))

I. THE JAPANESE EFFECTIVE FILING DATE

Japan, like Europe and to some extent Canada, places so many of the applicant's eggs in a "race to the courthouse" type of filing system, that this is the logical first point to start in any discussion of Japanese patent law.

A. Priority Filings to Gain One Precious Year

In the patent world of the 1990's, the patent application that is actaully prosecuted to grant is a second (or subsequent) patent application that claims a priority right based upon a substantively-complete but procedurally-soft priority filing. This is already the norm today for much of Europe and Japan, and is the accepted practice of a small minority of American applicants (however constituting the cream of the practice).

The American's "first to file" date may be dated back up to 12 full months to include the disclosure of an American (or other) earlier patent application.

Germans, French and all other foreign applicants operating under the Paris Convention are similarly entitled to a right of priority based upon their earlier filings. Japanese, too, can have an earlier domestic filing that can be rushed to the Patent Office in Tokyo that can then be replaced a year later by a regular filing.

The idea of the priority filing is to take early experimnetal results (or even paper and pencil chemistry that has not yet hit the laboratories) to a patent office anywhere in the world (in a Paris Convention state), and thus claim a priority right based upon this basic concept. Several of these priority applications may be filed.

Within one year of the first filing anywhere in the world, a "perfect" patent application is written and filed "everywhere", and this application claims a priority right based upon each of the several priority applications. For each "chunk" of disclosure found both in the perfect application and any earlier application date, the effective date for purposes of "first to file" is the date of filing of the first case with a common chunk.

Procedurally, the priority right is quite simple. As long as the actual filing in Japan is within one year from the first filing date, the applicant must (i) claim the priority at the time of filing in Japan (including identification of the filing date and serial number of the earlier application(s)); and (ii) file a copy of the original application(s) certified by the originating patent office. The certified copy can be filed up to three months later, and a translation should be filed.

B. Benefits of Being First to File

1. First to File Principle

As a "first to file" country, it is critical to obtain the earliest possible filing date: Being first to file among several independent inventors means two things.

The more self-evident benefit of being first to file is winning a right to obtain a patent should the invention be considered to represent a novel and unobvious advance versus the state of the art.

2. Patent-Defeating Right

a. The International System (Including Japan)

A more subtle victory is that by being first to file, merely by maintaining the patent application for 18 months from the first filing date, the patent application assumes critical defensive rights that operate as a shield to bar any third party from ever obtaining a valid, dominating claim. Thus, the patent application is automatically published in Japan 18 months from the first filing date, and from that moment on, a patent defeating effect retroactive to the filing date constitutes a bar to a third party's junior claim that would read on the disclosure in the first patent application.

To the extent that there has been no derivation from the junior filing party, the senior applicant's early filing date constitutes an absolute bar to newcomers, but only as to subject matter that directly reads on the disclosure of the patent application.

b. U.S. Unique System

The United States system follows a different system.

(1) Secret Prior Art

In one sense, the United States system works against its own inventors by creating a body of "secret prior art" to defeat claims to <u>different</u> inventions than disclosed in a first filing, even though the party coming along second has had no knowledge of the first party's invention. For example, workers in California and Massachusetts could be working on <u>different</u> inventions in the same field, with each filing patent applications at just about the same time. Each files a patent application to its <u>different</u> subject matter within a year or so of the other. Each secrecty takes steps in the pilot plant to commercialize the invention. Each diligently prosecutes his patent application, unaware of the other.

All of a sudden, the first to file receives his patent, and then, bingo, the second to file receives a rejection from the patent examiner stating that the heretofore secret patent application of the competitor has now been granted a <u>retroactive</u> patent-defeating effect constituting part of the state of the art as from the first filing date. Thus, judicial fiction is created that the second inventor had actual knowledge of the first inventor's work as from the first inventor's filing date for purposes of judging what would be "obvious" (and hence unpatentable).

The valuable investmests of the second inventor are shot, even though he has created subject matter totally independently of the first, and even though the subject matter may be totally different and nonoverlapping. Instead of two thriving competitors each with their own "better mousetrip" to bring competitively to the market, now there is only one.

This system of "secret prior art" is totally at odds with Japan and the rest of the world. In the international system, the state of the art for obviousness purposes is the date of publication, and not the filing date. (The only patent-defeating effect internationally as of the filing date is for directly conflicting subject matter which reads directly on the first filing.)

The second inventor who falls victim to secret prior art can still maintain his rights in Europe and Japan, but Americans who lose out at home are less likely to pursue the valuable foreign rights which are now too frequently forfeited.

(2) Denying Foreign Priority

The U.S. secret prior art effect for applications claiming priority based upon a Japanese, European or other foreign application is limited to the actual U.S. filing date, and not the foreign priority date. In this way, the odd situation can arise that a party has filed first in Canada and a year later in the United States, and yet a third party can squeeze in and obtain a patent that duplicates what is merely disclosed by the Canadian because the U.S. system does not give the patent-defeating effect as of the priority period.

This sitaution is not only an unfair windfall but also creates several problems. First, the matter is not absolute, because the Canadian who notices that a competitor with a junior filing date position has taken advantage of this loophole can often go to an expensive procdure knwon as patent reissue to add claims to the previously unclaimed matter, and thereby provoke a patent

interference. This patent interference permits reliance on the earlier date of invention under the Paris Convention.

Second, there is a widespread belief in international circles that the failure to give an international patentee a patent-defeating date for what he has claimed in his U.S. patent retroactive to the priority date constitutes a violation of Article 4B of the Paris Convention.

C. Six Month Grace Period

Like the United States and very few other countries, Japan has a grace period. Like the United States, the grace period excludes any priority based upon the Paris Convention, so that to meet the grace period there must be an actual filing in Japan, not merely a priority filing within the grace period. (However, the full equivalent of a national filing may be a Patent Cooperation Treaty application filed in the United States within the grace period, as long as that PCT application designates Japan.)

Unlike the United States one year grace period, the Japanese grace period is six months.

Unlike the United States, the Japanese grace period must be claimed at the time of filing through submission of a special gansho under Article 30, and within one month the particulars of the grace period prepublication must be submitted.

Also unlike the United States, a government publication such as a published patent application or patent is not eligible. Thus, if the American applicant files a Japanese patent application even

one day after his U.S. application has been granted, the Japanese application is absolutely barred.

Only one publication is excepted, so that if the applicant has published in two journals in the six month grace period, the second application constitutes a bar.

The application of the grace period also operates in a different manner from the U.S. grace period. Whereas the U.S. grace period denies any patent-defeating effect based upon the disclosure in that period, in Japan the grace period gives a right to claim the same subject matter as in the intervening publication, but any subject matter outside the scope of the intervening publication, but obvious in view of that disclosure, is barred.

Third party publications of independently created subject matter in the grace period, even if one day before the applicant's filing, cnostitute an absolute bar. The grace period has no applicability.

D. Classic U.S. Priority ("First Inventor" System)

Since the October 1, 1989, Canadian law revision to "first to file", only the Phillipines stands with the United States among all the countries of the world in having a so-called "first inventor" priority system.

1. Guarantee of a World-Wide Settlement for Some

Major domestic pharmaceutical companies today operate under a system of "first to file", because they more than any other

industry recognize the need for priority rights under the Paris Convention for obtaining a patent in Japan and Europe. Many of these same New Jersey giants are the staunchest supporters of the "first inventor" system. The enimgma of an industry totally committed to operating under first to file yet obviously supporting the "first inventor" system is easy to understand.

a. Precious Months Lead Over Foreigners

Even with optimum filing procedures, a major pharmaceutical company files a usual patent application only several months after an invention disclosure hits the desk of the patent attorney. There are procedures to follow, committee meetings to prioritise filings, and various formal hoops to jump through. By proving that one is "first to invent" in the United States, this means that the American inventor is able to prove priority in the United States before his filing date.

The foreign inventor lacks this same opportunity, because teh United States law territorially limits proof of a date of invention to the United States. Thus, even if the Canadian who is first to file also was first to invent, the Canadian's date of invention is worthless in a patent interference context with an American (unless the invention was made or propertly introduced into the United States).

b. Hopelessly Complex Interference System

If the American first inventor system is to be saved, immediate reform of the patent interference mess is of the highest priority. Today's system serves the major domestic and even

foreign-based multinationals by providing a trap against patent-naive smaller businesses, as well as any business that cannot afford the costs and years of uncertainty of a patent interference system.

The best tool to guarantee the position of the American big drug house is the interference system. Since it takes several hundred thousand dollars and many years of uncertainty for a contestsed interference to be concluded, it is unlikely that anyone other than a big drug house can stand the years of cost and uncertainty of outcome of a patent interference.

Even if the interference can be bankrolled and even if Wall Street is willing to look the other way for five years in a patent interference, the less patent-sophisticated concerns are unable to profit from the interference system and generally are outgunned by top interference lawyers retained by the top drug companies.

The net effect of the complexities and cost of the interference system is that while the very biggest and most established domestic chemical concerns are still able to rely upon the interference system to force settlements, the gap is generally very small vis a vis the multinational giants. In the case of several of the leading international pharmaceutical companies, including Japanese, the record for the international companies in interferences is a clear match for the best of America.

The loser is the Little Man from Little Rock, the small biotechnology business that is victim to both American and Japanese and other patent-sophisticated operations. While "first to file" may be an apparent answer, those favoring the first inventor system

clearly must recognize that first to file will be the inevitable answer if the Little Man from Little Rock is continually beaten up by patentees of all nationalities through an interference system he can neither afford nor understand.

c. World-Wide Settlement

Even though the interference system in the United States gives not direct rights to priority in foreign countries, the big drug house involved in an interference on the American patent is able to obtain a worldwide settlement of patent rights. Thus, while the foreign rights are generally owned by the first to file, as a result of the settlement of the U.S. interference, the winner of the U.S. patent interference is often able to enter all markets.

E. The Biotech Small Inventor as "First Inventor"

Being "first inventor" without being first to file provides a pitfalls on several fronts. To the extent that the second inventor has independently created his invention without derivation from the first inventor, the second inventor, no matter how junior in point of time, claims the entire world outside the United States if his priority application is first by even one day.

What is worse for the small American inventor is the very high level of patent sophistication of the Japanese biotechnology and pharmaceutical company of the 1990's. To meet the challenge of the American companies with their interference expertise, Japanese companies have become virtually as sophisticated as their American counterparts, winning on procedural quirks and strategies that used to be the exclusive domain of American companies. The victims of

this war for the best hired guns is the small American inventor who is no match for the large Japanese pharmaceutical company. Even with good counsel, American inventors often fail to file a patent application where they have completed a conception of their invention on paper, but mistakenly believe that they can defer the filing until after they have completed experimentation. In Griffith v. Kanamaru, 816 F.2d 624, 2 USPQ2d 1361 (Fed. Cir. 1987), Cornell's Dr. Griffith had the idea of certain pharmaceuticals before the effective patent date for Kanamaru, but failed to file quickly. Because Cornell could not show continuous laboratory diligence to make the compounds, the priority enjoyed by Dr. Griffith was limited to a worthless "conception" date. This case was followed in the December 11, 1989, Magistrate's opinion in Amgen, Inc. v. Chugai, where Genetics Institute was denied priority in part because it failed to show continuous diligence in reducing its erthropoietin invention to practice. Quoting from Griffith, 816 F.2d at 628, the Magistrate in Amgen stated that ""[o]ne having the first complete conception of an invention cannot hold the field against all comers by diligent efforts, merely, to organize and procure sufficient capital to engage in the manufacture of his device or mechanism for commercial purposes."

II. FILING PROCEDURES IN JAPAN

A. Simpler Filing Procedures

Japanese patent application filing procedures are much like those for European countries and many other countries around the world. Since these filing procedures are much simpler than in the United States, this facilitates easier filing in Japan than here. While Americans benefit from this simpler filing system when they

file an application in Japan under the Paris Convention, the American priority date is based upon the earlier filing date in the United States under a more complex procedure. This discrepancy permits Japanese on the average to gain weeks or days of priority versus Americans.

A classic example is the inventor's oath or declaration which is required in the United States either at the time of filing or shortly thereafter, while Japan does not have this requirement. The American inventor who receives his application with the oath for his signature typically will change the application papers one or two times, and this may delay filing by days or weeks. Since the Japanese do not have this formal requirement, this means that the Japanese priority application filed in Japan has an inherent advantage of the days or weeks lost by the American who goes through the oath formalities. (The Japanese goes through these same formalities a year later when he files in the United States, but since the priority date is key, it is applicant who files first in the United States who is the loser.)

B. Filing by a Japanese Benrishi

The good news is that the Japanese benrishi are at the very top of the world patent profession in terms of qualifications to join the profession and overall excellence. The bad news is that there are too far few to service American biotechnology interests.

The English text to be used as the application is given to a local patent attorney in Tokyo or Osaka, who translates the application into Japanese and then can be relied upon for taking care of the various formal matters. The Japanese patent profession

is one of the most reliable in the world. The benrishi who are registered to practice as part of the Japan Patent Attorneys Association (JPAA) have survied a fair, blind, three stage examination with a pass rate of about two (2) percent. This is by far the most difficult examination of any patent profession in the world.

With a difficult test resulting in a small profession, coupled with only a minority being in a position to service foreign clients and still fewer able to work in the field of biotechnology, there are effectively less than fifty persons at the first level of prosecution in all of Japan who are qualified to accept biotechnology work from Americans. There are only about five firms with twenty or more benrishi with persons in this category, one in Osaka and the reaminder in Tokyo.

With the scarcity of talent in Japan, and with conflicts barring new certain new clients to most of these firms, the problem for the American biotechnology company is self-evident.

C. The Unique Problem of Translations

1. No Provisional English Filings

In the patent world of the 1990's, English has already become the main language for patent prosecution for first tier protection. Provided the expediency of a European Patnet Applciation is included as part of a filing strategy, patent applications can be filed in English and prosecuted up to grant in English for protection in Germany, France and a total of more than ten other European countries, plus Canada, South Africa and other former

Commonwealth countries. (Expensive translations in Europe are due when the patent is granted.)

Japan, however, remains a unique problem for Americans because not only must the application be translated into Japanese, the translation constitutes the original filing document for Japan. Filing in English gives no rights, even of a provisional nature.

As a result, it is imperative that the American today send his patent application to Japan as soon as possible, preferably two months prior to the deadline, but in any event a few weeks in advance.

Failure to provide sufficient time for a translation is a guarantee that mistranslations will occur, often of a major nature. No matter how excellent the benrishi, no person can "instantly" translate a case into good Japanese. Horror stories abound where an application is faxed to Japan on the last day, with teams of different benrishi and their staffs each taking several pages, and then quilting the pieces together, or of cases where only a part of the case could be completed before the gun went off at midnight of the deadline day.

2. The Patent Cooperation Treaty

Where there is insufficient time to permit a thoughtful translation, the far better course of action is to safeguard Japanese patent rights by filing a PCT application. The PCT application is filed in Washington, D.C., in English, and the entire Japanese language translation (and all other Japanese)

formalities can be deferred to 30 months from the first U.S. filing date.

To be sure, PCT is very expensive if used solely for Japan. Presumably, PCT would be used to defer all the foreign filing expenses for most of the Common Market countries and other parts of Europe by filing a European application (protection beyond the Common Market includes Switzerland, Sweden and Austria, but excluded aer EEC countries Greece, Ireland and Portugal), plus South Korea, Canada, Australia and -- in a time of perestroika -- both Hungary (the leading socialist country for pharmaceuticals) and the Soviet Union.

3. International "Official Languages"

The long range solution that is up to Executive Branch in negotiations with foreign countries is the designation of several official languages that can be used in any country for purposes of filing. Efforts at WIPO would permit filing in any language to obtain a filing date. These efforts have met strong opposition by some European countries and Japan.

The reason for the opposition is natural. The proposal in some way goes too far by permitting a filing in any language, and not far enough in terms of flexibilty in correction of translations that must in the end be made.

Instead of attempting to reach a compromise that would permit Americans a meaningful improvement in the international system, there is now an extremist proposal under circulation that would simply make English a worldwide official language. The good news

is that this would solve all of America's language problems. The bad news is that the proposal is insensitive and in the end may kill constructive compromises that are under discussion.

An "official languages" proposal to respect all major countries and their languages is suggested as a reasonable compromise. As a minimum, there should be six official languages under any such proposal, the three official languages of the European Patent Office (French, German and English), Russian, Japanese and Spanish. To the extent that territories with different official languages would join an international system, then the list of official languages could be expanded.

By filing in any official language, a filing date would be guaranteeed. Then, a translation into a local official language could be required within 16 months (in time for any national publiation at 18 months). If there are any errors in the translation, they should be freely correctable up through the grnat of the patent, subject to intervening rights to persons who relied upon translation errors.

III. THE 12TH THROUGH 18TH MONTHS

A. Temporary Deferral of the Examinaton Request

Optimum filing procedures in Japan take advantage of the right to file the application without a formal request for examination. By deferring this request (as well as deferring the substantial fee that is required), good things happen.

First, an absolute right to amend the application one time before examination is reserved, even for years later, simply by deferring the examination request. Then, at the time the examination fee is paid, there is an absolute right to concurrently file an amendment. (This procedural right is different from the substantive law for amendments that is in effect from the first day of filing up through the grant.)

Second, the applicant can better time his prosecution. For example, if the applicant wants to start prosecution only after the counterpart European and American applications have been granted, he can do so. Under this advantageous approach, the examination fee coupled with an amendment tailored to the results of the European and U.S. examinations can be filed before the Japanese examiner is permitted to act on the case.

B. Minor Error Correction through the 15th Month

Up to 15 months from the U.S. (or other first) filing date, a window is open for correction of the specification. Any amendments may be made that do not change the "gist" of the invention.

C. Preserving Rights to Minor Improvements

Generally, the first publication of the invention anywhere in the world occurs substantially simultaneously in Munich, Tokyo and other patent offices, or in Geneva (if the PCT is used), 18 months from the priority date.

Before the first publication, there is a window of opportuntity for American inventors to preserve Japanese rights to even trivial improvements that otherwise would be lost under Japanese law.

1. Identifying Gaps in Protection

The starting point is a timely review before the publication of the invention of the claims of the Japanese patent application.

Could I as a third party devise an embodiment of the invention outside the literal wording of the claim? If the answer is "yes", then this embodiment should be considered a pag in proection, because the strict Japanese claim system will likely lead to the result that any embodiment outside the scope of the claim is free to the public. (Another answer would, of course, be to see whether the existing claims can be broadened to include the embodiment.)

The next step is to determine whether there are any potentially important commercial embodiments within the scope of the claim wording, but which do not correspond to any examples in teh specification. Or, where the embodiment reaches a slightly different result than the embodimments disclosed in the specification.

Other gaps may be a failure to have claimed a combination that includes the invention. For example, if a particular pharmaceutical product disclosed for one use has several obvious other uses, these constitute gaps in protection.

For any of these embodimnets differing from the disclosure of the preferred embodimnets of the patent, there is a serious question concerning a possible gap in protection.

2. Plugging the Gaps

At least one day before the first publication of the invention, all of the "gaps" should be filled in by filing in the United States a patent application that discloses subject matter to the embodiments outside the first case, as well as the embodimnets that were not found in the first case.

As long as the same applicant files the second patent application, the actual filing in Japan can be deferred for one year under the Paris Convention.

a. One Application for Many Inventions

The second application can include all the various "gap" inventions, even though this violates the policy of "unity of invention". This is true both for the U.S. application as well as the Japanese application filed one year later.

The unity requirement only comes into play at the time of the examination by the U.S. or Japanese Patent Office.

b. Artichoke Prosecution of the Second Case

There may be, say, five or ten or more separate inventions in this second case. In Japan, the second application would be

deferred until such time as it appeared that one of the inventions should be examined in view of the actaul commercial situation. Then, like the leaves of an artichoke, one by one inventions can be examined. (The remainder in each case can remain dormant in a divisional application.)

3. The Fusion Problem: Unplugged Gaps

The most notorious misunderstanding in the patent field for the 1980's involved the pioneer invention by Maryland's little David, Fusion Systems, that had its invention in Japan "stolen" by the Tokyo Goliath Mitsubishi. A close examination shows that had David sought early legal advice from competent Japanese counsel, the problem would never have happened. (In fact, the original benrishi was replaced some time ago.)

One of the key Fusion mistakes was the failure to create an Artichoke. Quite apart from the offensive value of a second tier filing, any Mitsubishi filing to second tier inventions would have been barred to Mitsubishi.

What Mitsubishi did (and what sophisticated companies of all nationalities do) was to immediately start research on the Fusion invention as soon as it learned about the technology, presumably thanks to the 18 month publication. Clearly, once the invention was public, tiny Fusion was no match for Mitsubishi to develop improvement inventions. But, had Fusion had a patent application on file when it had a monopoly on the information (i.e., before the publication), then it could have barred the obvious modifiations made by Mitsubishi.

Had an Artichoke application been on file in Japan with a priority date earlier than the Mitsubishi filings, each of the Mitsubishi filings reading on the Artichoke would have been barred even if the Artichoke were never examined but merely maintained until publication.

IV. THE CRITICAL FIRST ACTION

Key to ex parte prosecution is a response to the Examiner's first office action. While there are many similarities between U.S. and Japanese, there are also subtle differences:

A. A Four Month Window

Japan has a system of "windows" for making changes in the patent application. The usual window prior to prosecution before the Examiner is the date of filing the examination request.

The window reopens for the four months from the date of the Examiner's rejection. If an amendment is to be filed, it should be done in this window. A "Supplemental Amendment" outside the window is not permitted.

B. Avoiding a Fatally Narrow Interpretation

1. Kinhangen: Narrowing through Overargument

Too often, American attorneys will take American arguments from American patent prosecution and order or more than politely suggest to the benrishi that he respond to the Japanese action with the same American arguments.

To the extent that the American arguments are not even necessary for allowance in Japan, the foolishness of this course of action is self-evident. For example, there may be a third party's prior-filed patent application that in the United States constitutes prior art for purposes of obviousness by virtue of the earlier filing date. But in Japan, this same prior art may only have a novelty-defeating effect, and not be a part of the state of the prior art for determining obviousness.

An argumnet that a feature within the claim is important in the United States may have no effect on the scope of protection granted under an analysis of the literal scope, but in Japan this may constitute kinhangen to limit the scope to the exclusion of some literally covered embodimnets.

2. The Indispensible Elements Rule

A cardinal mistake of U.S. practitioners who "dictate" prosecution of the Japanese application is a failure to abide by the Japanese "indispensible elements" rule, which is not a part of the United States law.

For optimum protection, it is essential that if the claims as filed have not been drafted to meet this requirement, at the time of the response to the Examiner's rejection, then the claims should be drafted to eliminate all limitations other than those which are "indispensible" to defining a patentable invention over the prior art.

Under U.S. law, a claim may recite several elements, including some that are critical to patentability as well as others that are not so critical. Under Japanese law, there is a requirement that the claim exclusively recite only the critical elements ("indispensible elements"). The penalty for violation of this rule is indirect: The District Court judge in an infringement action will interpret every element of a claim as being "indispensible", because the law requires the applicant to recite only the indispensible element in the claim. Perhaps the most notorious example from the 1970's involved a complex chemical process where the patentee American Cyanamid properly recited the truly critical elements in the claim, but fatally included a conventional step with a claim limitation that this step be conducted at a temperature of at least 20° C. Mitsubishi Kasei, the accused infringer, was able to totally avoid infringement liability simply by duplication of the entire process, including the conventional step, but by carrying out the conventional step at 17.5° C.

C. Citation of Prior Art by Applicant and Third Parties

Japan has no requirement to cite prior art to the Examiner. Therefore, there is nothing in Japanese patent practice akin to the American "duty of disclosure" that compels an American applicant to cite prior art. As a practical matter, however, if there is prior art that will be readily apparent to a potential opponent, it is worthwhile to cite such prior art on a voluntary basis. To cite the prior art now in the ex parte prosecution phase is to permit immunization of the patent application against an effective attack on the same prior art at a later, inter partes opposition stage.

Third party citation of prior art to the Examiner at an early stage is now fully permitted and suggested by the Japanese Patent Office. However, careful opponents are more likely to save their best ammunition until after the ex parte examination phase is over, to squarely shoot at the provisional patent in an opposition.

D. Interviews

A personal interview with the Examiner by the benrishi is an extremely useful tool that should be considered on a routine basis. Since the majority of patent application prosecution in Japan today is carried on by persons not licensed to practice at the Japanese Patent Office (particularly for domestic applicants), interviews are much less frequently conducted in Japan than the United States.

The value of interviews is exemplified by Japan's largest pharmaceutical company that is situated in Osaka -- a three hour shinkansen express trip away. That company both frequently dispatches its patent staff members to Tokyo and maintains a permenannt liaison office with a manager level member of the patent department just four subway stops away on the Ginza Line from the Japanese Patent Office.

While there may be justification for a non-interview strategy on a case by case basis, for very important cases there should be some exceptional reason to justify not having such a personal interview.

E. The Kokoku and the Opposition Period

After the give and take of one or more Examiner's actions, the patent application that has been properly prosecuted and contains patentable subject matter receives a notice that the application is to be published for purposes of any opposition.

Several important points should be noted:

1. The Patent Right Exists from Kokoku

From the date of the kokoku, the patent right is in existence. A lawsuit may be brought from this time forward, with or without an opposition. Should the defendant request a stay of proceedings in an infringement suit due to an opposition, this request may be granted, but this is not necessarily so. For example, in the Osaka District Court today there is ongoing litigation on the tissue plasminogen activator patent owned by Genentech.

2. Three Month Period for Opposition

The three month period for opposition in Japan is extremely short, relatively to the unlimited time for seeking reexamination in the United States and the nine month opposition period in Europe.

Since it is difficult to monitor Japanese publications, and there are inherent delays in translations, an American must monitor inventions from the 18 month publication (kokai), so that he is prepared for the opposition period.

3. A Vigorous Inter Partes Contest

The popularity of oppositions in Japan derives from the fact that the opponent is given a fair hearing to present his views to the Office.

The opportunity to present prior art and other arguments in an opposition proceeding is a major reason that the Japanese patents which survive the opposition period (with or without an opposition) have such high respect later in enforcement proceedings. Thus, while it is theoretically possible to challenge the validity of a Japanese patent even after grant, the chance of successfully doing so is very low.

F. The Final Grant and Patent Term

Without an opposition, the patent is quickly granted. With an opposition, the final grant is delayed until the opposition period has expired.

The term of the patent is 20 years from the filing date in Japan (exclusive of the extra one year period of the Paris Convention priority year). If for some reason the patent is granted less than five years from the filing date, then the term of the patent expires 15 years from such grant.

There is also a patent term restoration for certain regulated chemicals, particularly pharmaceuticals.

G. Appeal Procedures

Whether the applicant loses before the Examiner or is unsuccesful in an opposition proceeding, in either case the applicant has a right of appeal to a Patent Office Board. From there, the dissatisfied applicant has a right of appeal directly to the Tokyo High Court. (The Tokyo High Court is an intermediate level court that hears appeals from the Tokyo District Court in all areas; there is a right of appeal to the Supreme Court.)

V. PROCEDURAL AND SUBSTANTIVE RULES FOR CLAIM AMENDMENTS

A. Substantive Rules for Amendment

1. The Rules Prior to the Kokoku Stage

Up until the decision to publish an application for opposition (kokoku), the rules for amendment are extremely liberal, perhaps more so than in the United States. Claims may be freely broadened. Matter may be added to the claim that does not change the "gist" of the invention. The "gist" standard is at least as broad as the U.S. standard for a "written description" basis for any new matter.

2. Limitations After Kokoku

After the decision ot publish for opposition, the applicant is barred from any amenmdnet that would broaden the scope of the claims. Thus, even though in the Mitsubishi-American Cynamid dispute there was no criticality in a temperature limitation of at least 20° C (as in the claim), by the time litigation has started, it is too late to delete such a limitation.

3. 30 Days from Notice of Opposition

Where an applicant finds that his claims are fatally narrow for meaningful coverage, one loophole exists after the kokoku. This is the right to file a divisional application within the 30 day period after an opposition has been noticed. Apparently, some companies have created an opposition solely for the purpose of giving a right to a divisional, and hence a broadening of the nvention.

B. Procedural Windows for Amendments

Only during specified time windows is an amendment permitted of any kind. Once the application is more than 15 months old (dated from the priority date), there are two main windows in ex parte prosecution. First, concurrently with the examination request, an amendment may be filed. (Premature filing of an examination request, such as concurrently with the filing of the application, is generally not recommended for other reasons, and certainly the forfeiture of this window for amendment is a serious mistake.)

Later, during prosecution, there are brief windows for amendment, which may be as short as 30 days (e.g., the deadline for filing a divisional after an opposition) or as much as four months (the period for response to the Examiner's action).

VI. PATENT LIGITATION

A. Patent Infringement

1. Specialized IP Chambers

The majority of patent litigation is in a IP specialized chamber of the Tokyo District Court or the Osaka District Court. Nagoya has some patent litigation, with a very small amount of patents being enforced throughout Japan.

The patent litigation is limited to a consideration of patent infringement, as the District Courts have no jurisdiction over patent validity.

2. Appeals Courts

The bulk of all patent appeals go to a specialized IP chamber of the Tokyo High Court, which hears appeals from both the District Court in infringemnent matters, as well as all appeals from the Patent Office, including trials for invalidity. The Osaka High Court also has a specialized chamber to hear patent appeals from the Osaka District Court.

An appeal as a matter of right to a petit bench of five Supreme Court justices also exists. A grand bench has all fifteen judges.

B. Trials for Invalidity

In parallel with the lawsuit for infringemnet in either the Tokyo, Osaka or some other District Court, the accused infringer will generally seek a ruling of invalidity at the Patent Office.

A right of appeal in an invalidity suit is to the Tokyo High Court.

Generally, the District Court will not suspend an infringement suit, but will decide the infringemnet issue even if there is an ongoing invalidity suit. However, if the claims read on hte prior art, the District Court judge has the discretion under a pair of Supreme Court decisions of more than 25 years ago to simply hold that the claims should be limited to their examples -- which means that the claims are too narrow to be enforced.

C. Trials for Amendment

Prior to the 1987 law change, there was only a single claim system in Japan. While a single claim in a patent could for some years have several "dependent claims", these were sham claims introduced so that Japan could appear to comply with the Patent Cooperation Treaty requiremnet for multiple claims.

Since the patents in litigation today were filed before the 1987 law change, the old single claim system is the one that will be used for cases now in court. Only "claim 1" (or some second, independent claim to a different invention) can be directly enforced in the court.

If the patentee wishes to either narrow the claim, or have one of the dependent "claims" enforced, it is necessary that he submit the application to a Trial for Amendmnet at the Patent Office. This Trial for Amendment proceeds in parallel with any Trial for Invalidity, both in terms of wno hears the first instance proceedings at the Japanese Patnet Office and the route of appeal to the Tokyo High Court.

VII. RELIEF

A. Preliminary Relief

Preliminary injunctions may be sought in a separate proceeding that should precede the regular injunctive relief proceedings. In Tokyo, such preliminary relief was obtained in the famous 1987 "Roundup" case where Monsanto successfully enforced its patent much more quickly than in most other countries, including the United States (where the litigation had started years earlier and where the Japanese victory stimulated the parties into a worldwide settlement even without a final American verdict). In Osaka, the District Court improperly holds both the preliminary and regular proceedings simultaneously, effectively destroying the chance for very early relief in Osaka.

B. Damages

Damages are based on a more reasonable award system than the United States. Some would consider the damages too low to effectively compensate a patentee against an accused infringer, at the opposite end of the spectrum from what many believe are too high awards in the United States.

VIII. CLAIM CONSTRUCTION FOR GRANTED PATENTS

The heart of any patent today in any country is the claim or claims that generally appear at the end of the patent application. Like the deed to a piece of real property, the claim defines the metes and bounds of intellectual property claimed by the patentee.

Under Japanese patent law, claims are construed far more narrowly than in the case of the United States. Two claims, identically worded, one in Japan and one in the United States, lead to different results:

If the accused infringing embodiment is within the wording of the claim, in the United States this is generally conclusive as to a finding of infringement. Intervet America, Inc. v. Kee-Vet Laboratories, Inc., 887 F.2d 1050, 12 USPQ2d 1474 (Fed. Cir. 1989). In Japan, claims are frequently construed in a narrow fashion so that, for example, embodiments that are within the scope of the claim but not supported by working examples may be deemed outside the effective scope of protection.

It is considered a priority of the WIPO exercise in Geneva to provide a uniform claim interpretation system that provides broad coverage in Japan and other systems as well. Article 304 of the Draft Treaty (1989) is designed to permit Japan to modify its domestic law to reach the same broad interpretation of claims that is found in both the European Patent Convention and United States patent law. (See APPENDIX: THE WIPO PATENT INTERPRETATION ARTICLE.)

APPENDIX III: THE WIPO PATENT INTERPRETATION ARTICLE

(excerpts from Wegner, Comparative Patent Law (1990))

Article 304 ("Extent of Protection and Interpretation of Claims") has been greatly revised in the 1989 Draft Harmonization Treaty. The origins of Article 304 stem from U.S. proposals to introduce a reasonable scope of protection outside the literal wording through the doctrine of equivalents, while precluding narrowing. The wording of the Article reflects the U.S. "all elements" rule of Pennwalt Corp. v. Durand-Wayland, Inc., 833 F.2d 931, 4 USPQ2d 1737 (Fed. Cir. 1987) (in banc), when the language was proposed. Cf. Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 9 USPQ2d 1962 (Fed. Cir. 1989).

The general principle is first stated in Article 304(1) provides that the scope of protection "shall be determined by the claims, with due regard to the description and drawings." At the Seventh Session, the French offered a substitute proposal that received general acceptance; the EPC claim interpretation protocol was woven into the this proposal so that it will be clear to European judges that the broad EPC claim interpretation principles could be continued. (There is a viewpoint in some European circles that in some ways the European interpretation is even broader than that in the United States.)

There was controversy over Article 304(2), which provides for expansion of the claim to cover equivalents. The text as presented in the Draft

(a) Any claim shall be construed to cover not only all the elements as expressed in the wording of the claim but also equivalents of any such elements.

(b) An element shall be considered as being equivalent to an element as expressed in the wording of the claim if, at least in regard to the invention, it functions in substantially the same manner and produces substantially the same result as does the element as expressed in the wording of the claim.

Controversy over Article 304(2) at the Seventh Session centered on a dispute among European delegates that the definition of the doctrine of equivalents in Article 304(2)(b) satisfied only the U.S. definition, but did not accommodate a possibly broader definition under existing Dutch (or perhaps also other European) law. The Dutch did not want to see a forced narrowing of claim interpretation principles while at the same time did not want to force the United States to broaden its interpretation principles. The Dutch therefore proposed that there be alternative definitions that would satisfy either the U.S. or European interpretation.

A "Franco-Dutch" compromise incorporating the French Article 304(1) and a Dutch Article 304(2) represents a distinct improvement in the Draft Treaty; it remains to be seen what wording will be proposed by WIPO in the Draft Treaty for the Eighth Session.

Prosecution history estoppel is taken into account under Article 304(3) which states that "[w]here the applicant * * * has, in the description or during any procedure concerning the application or the patent, expressly stated that a specific

equivalent element is not to be considered as covered by a claim, [the provision on equivalents in Article 304](2) shall not apply to such an equivalent." The French considered this to be too narrow in that there is a mandatory application of estoppel. To permit the French to retain a broader interpretation of patents while also permitting U.S. courts to apply a stricter prosecution history estoppel, the "shall" is changed to "may" in the French substitute.

In addition, Article 306(8) provides that a broad interpretation is not permitted in patent enforcement proceedings if that "is different from the extent of protection asserted by him in any such previous proceedings."

To overrule the Manmade Diamond case, Article 304(4) states that "[i]f the patent contains examples of the embodiment of the invention or examples of the functions or results of the invention, the claims shall not be interpreted as limited to those examples * * *."

Article 304(4) further states that "the mere fact that a product or process includes additional features not found in the examples disclosed in the patent, lacks features found in such examples or does not achieve every objective or possess every advantage cited or inherent in such examples shall not remove the product or process from the extent of protection conferred by the claims."

Less important are paragraphs (5) - (7): Article 304(5) states that "[a] claim for an invention that consists of a combination of inventions shall not provide protection for any of those inventions taken separately." Article 304(6) states that

"[a]ny reference to a drawing or part of a drawing in a claim shall be construed as illustrative only and shall not be construed as limiting the protection conferred on the invention to what the drawing or part thereof shows, unless the claim clearly indicates otherwise." Article 306(7) states that "[t]he abstract * * * shall not be taken into account for the purpose of determining the protection that is conferred on an invention by the patent."

APPENDIX: LETTER CONCERNING THE RESEARCH EXEMPTION

Letter regarding the Patent Research Exemption (H.R. 4970), July 14, 1988 to the Honorable Robert W. Kastenmeier Chairman, Judiciary Subcommittee on Courts, Civil Liberties and the Administration of Justice United States House of Representatives, Washington, D.C. 20150 from Harold C. Wegner

Dear Mr. Chairman:

Your proposed legislation, H.R. 4970, admirably attempts to clarify the research exemption for patent law. But, the goal should be to codify the case law holdings, particularly those from the landmark opinions of Justice Story which created an experimental use doctrine, as explained by Professor Robinson, 3 Robinson on Patents §898 (1890).

The Federal Circuit has never been squarely faced with this issue, although including as dictum a narrower approach in Roche Products v. Bolar Pharmaceutical Co., Inc., 733 F.2d 858, 221 USPQ 937 (Fed. Cir.), cert. denied, 469 U.S. 856, 225 USPQ 792 (1984). Some trial courts -- but not the Federal Circuit -- have narrowed the definition of experimental use.

* * *

The other aspects of H.R. 4970 as marked up on July 13, 1988, require separate consideration, outside the scope of this letter.

Creation of the Experimental Use Doctrine

The Constitution mandates that any federal patent system "promote the progress of * * * the useful arts". Article I, Section 8, Clause 8. Nothing is more fundamental than providing the earliest conveyance of the latest scientific information so that all can benefit from that knowledge. Central to the patent system is the right to use that scientific information to create new and better inventions in competition with the patented invention.

A contrary result would be unthinkable: The framers of the Constitution clearly could not have envisioned shutting the door to further research for the long period of the patent grant.

Justice Story, the leading patent jurist from the formative years of the early nineteenth century, created the experimental or research exemption in Whittemore v. Cutter, 29 F. Cas. 1120, 1121 (No. 17,600)(C.C.D. Mass. 1813) and Sawin v. Guild, 21 F. Cas. 554 (No. 12,391)(C.C.D. Mass. 1813).

Professor Robinson provides a perspective from the late nineteenth century, which clearly shows that experimental use is to benefit the employer's knowledge -- which is research manifestly with a commercial purpose in mind:

> [W]here [the invention] is made or used as an experiment, * * * the interests of the patentee are not antagonized, the sole effect being of an intellectual character in the promotion of the employer's knowledge * * * *

3 Robinson, The Law of Patents for Useful Inventions §898 (1890); emphasis added; followed by 4 D. Chisum, Patents, §16.03[1] (1988).

Business (Regulatory) Testing is Not Exempt

Business testing clearly is not an experimental use, as quite correctly held in Roche Products. (Subsequently, some business testing has been exempted by statute, 35 USC §271(e)(1) of the Drug Price Competition Act, Public Law 98-417 (1984).)

In Roche Products, patentee Roche had marketed its patented drug Dalmane for many years, with great commercial success based on its exclusive position as the pioneer patentee. Infringer Bolar wanted to copy that very drug and go into competition immediately upon expiration of the Roche Products patent. To do this, Bolar needed approval from the Food and Drug Administration, which involved testing prior to the expiration of the patent. It was this business-oriented regulatory testing that was the subject of the controversy in Roche Products. Bolar thus was testing not for its own scientific or other knowledge, but only to satisfy stringent regulatory tests which were a condition for governmental marketing approval.

That the holding in Roche Products was a correct interpretation of the experimental use exception is underscored by foreign infringement decisions dealing with regulatory testing, particularly in countries where the experimental use exception is more firmly embedded in the statutory scheme. The best example is the Monsanto worldwide litigation involving Stauffer's regulatory testing of a herbicide within the scope of a Monsanto patent. Here, the testing was to gain governmental approval for commercial marketing in countries such as Germany and Japan. Such testing was found to be an infringement in courts in both Düsseldorf, Hindersmann, Stauffer Chemical Europe S.A. et al., 18 IIC 407 (1987), and Tokyo, Monsanto v. Stauffer (Tokyo District Court 1987).

Professor Robinson draws a correct distinction between this type of business-oriented testing and true experimental testing:

> [W]here [the invention] is made or used as an experiment, * * * the interests of the patentee are not antagonized, the sole effect being of an intellectual character in the promotion of the employer's knowledge * * * *. [I]f the experiments are conducted with a view to the adaptation of the invention to the experimenter's business, the acts of making or of use are violations of the rights of the inventor and infringements of the patent.

3 Robinson, The Law of Patents for Useful Inventions §898 (1890); emphasis added.

Dictum in Roche Products Dealing with Experimental Use

Roche Products would have been an excellent statement of the law, if it had merely dealt with business testing, and not gone off into dictum dealing with the scope of the research exemption.

Thus, the problem with the Roche Products case is not the holding, but rather sweeping dictum which indicates that virtually all uses of a patented invention constitute an infringement. This is superficially reconciled with the opinion of Justice Story in the Whittemore case, but only by limiting the Story doctrine to "philosophical" use of an invention, and using a modern definition of "philosophical" -- not one from the era in which Story wrote. "Philosophical", in the era of Justice Story, was "characterized by

learning or the spirit of inquiry". Webster's Third New International Dictionary, definition 1 Archaic for "philosophical", p. 1698 (1986).

The distinction drawn in this dictum, therefore, does not stand scrutiny. The patentee Roche Products never argued this distinction, focusing on the business nature of the testing. * * *

Putting Americans on Equal International Footing

Today, patents are granted in parallel in the United States, Europe and Japan, with virtually identical disclosures and similar claims. The researcher in Kyoto or elsewhere in Japan is free to use a patented invention in his laboratory to create new products outside the scope of the first patent. So, too, the researcher in Köln or Düsseldorf. It is clearly against public policy to proscribe American R&D from use of patented inventions solely for research purposes to create new products.

What happens if Americans are prohibited from using a patent for research purposes, while those in Japan and Europe are not? Clearly, this would drive research to the safe havens of Europe and Japan, away from America.

Protecting the Manufacturers of Research Tools

One concern expressed in some quarters is that companies in the business of selling research tools could reap a windfall by a broadly worded research exemption. Thus, a broadly worded definition could permit sales of research tools without regard to patent rights. That concern is justified. Thus, the proposed wording carefully guards against such a possibility, as exempting only the "manufacture or use [of] an invention to study, evaluate or characterize that invention or to create a product outside the scope of the patent." First, sales would not be covered. Second, neither would the business of making research tools be exempt, as that is a business purpose, i.e., the manufacture or use is not for the purpose to "study, evaluate or characterize that invention * * *."

A Solution Consistent with International Principles

Both Japan and Europe have well-defined experimental use doctrines, generally codified. Japanese law, Article 69(1), in Tanabe & Wegner, Japanese Patent Law, p. 289 (1979), states that: "The effects of the patent right shall not extend to the working of the patent right for the purposes of experimentation or research." J. Straus, "The Principle of 'Dependence' under Patents and Plant Breeders Rights", Industrial Property, pp. 433-443 at 440 (December 1987), quotes CPC Article 31(b): "[T]he rights conferred by a patent [in Europe] do not extend to 'acts done for experimental purposes relating to the subject matter of the patented invention.'"

The generally accepted international view favoring a broad policy to permit use of a patented invention for research is explained by Straus:

> By taking the information and the incentive function of patent protection into account, this limitation guarantees the freedom to all skilled in the art to test and examine patented inventions, without the consent of the patent owner even during the term of protection, to establish the invention's utility, working advantages and disadvantages, and above all to develop, on the basis of the knowledge so acquired, improved (patent-dependent) or new (patent-independent) solutions. * * * [T]here seems to be a general consensus that experiments with a patented invention in order to develop improved or new solutions do not constitute patent infringement, as long as they are limited to the subject matter of the patented invention. Whether the commercialization of results obtained by experiments with a patented invention is to be regarded as an infringement of the prior patent ultimately depends upon the question of whether they are to be considered dependent.

Straus, supra; footnotes omitted, including citations to Bernhart/Krasser, Lehrbuch des Patentrechts, 4th ed., footnote 64, p. 574 et seq., Munich, (1986); Benkard (Bruchhausen), Patentgesetz - Gebrauchsmustergesetz, 7th ed., footnote 64, p. 378, Munich

(1981); Chrocziel, Die Benutzung patentierter Erfindungen zu Versuchs- under Forschungszwecken, p. 186, Cologne (1986); and Crespi, 1986 EIPR 264.

Legislation to Deal with the Business Testing Issues

The latter portion of H.R. 4970, Sec. 2, 35 USC §271(g), deals with a business exception for animal regulatory testing. To include in one section of a bill both a research or experimental exemption with a business testing exemption is to mix apples and oranges. Whether business testing exemptions are necessary will first depend upon what tests the government will require to permit marketing of genetically-modified animals such as Harvard's mouse. Is there a very long regulatory period? What kind of tests will evolve?

Only when the true scope of regulatory testing is mapped out will it then be possible to consider legislation to deal with whatever practical problems may or may not emerge.

To put the animal area on a par with the drug testing by generics in the Drug Price Competition Act, Public Law 98-417 (1984), is entirely premature: The first animal patent will not expire until the year 2005; and, none has yet been commercialized as a pioneer, so as of now, there is nothing to test for copying purposes. Even if it takes, say, five full years for "me too" regulatory testing, this would mean that the first regulatory testing for a "me too" product for post-expiration marketing would be in the year 2000.

Whatever efforts should be focused upon animal patenting should be in the regulatory area to determine the conditions under which a prospective marketer may put his new animal on the market.

* * *

If and when legislation becomes necessary, a solution along the lines proposed in this letter would be advisable, patterned after Professor Robinson's interpretation of the Whittemore and Sawin cases.

* * *